



# Placebo or Panacea: The FDA's Rejection of ImClone's Erbitux Licensing Application

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# Placebo or Panacea:

## The FDA's Rejection of ImClone's Erbitux Licensing Application

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## Abstract

This paper draws upon the media reports, congressional hearing testimony, and company press releases to recount events surrounding the FDA's refusal to issue a license to ImClone's cancer drug Erbitux, late in 2001. Erbitux was granted fast-track status by FDA, and was evaluated under the agency's accelerated approval process. Despite hype about the drug's effectiveness in fighting certain types of cancer, the FDA found numerous and considerable problems with the licensing application, and in particular with the conduct and documentation of the main registration trial. The paper discusses the possibility that ImClone's public statements may have misled investors, and the ability of the FDA and the SEC to oversee these disclosures. Finally, recent changes in the FDA approval process are addressed, as well as the current state of ImClone's continuing attempts to gain licensing approval for Erbitux.

## Part I: Introduction

### The Erbitux Rollercoaster

On December 28, 2001, the U.S. Food and Drug Administration faxed a "refusal to file" (RTF) letter to ImClone Systems, notifying the company that the FDA would not accept ImClone's Biologics License Application (BLA) for its cancer drug, Erbitux.<sup>2</sup> Less than two weeks earlier, ImClone was named one of seven biotechnology companies included for the first time on the NASDAQ 100, and in the preceding months Erbitux had been the subject of several glowing stories in Business Week, the L.A. Times, and elsewhere. ImClone's stock hit a high of \$75.45 on December 6, and closed at \$62.96 on December 21, just one week before the Erbitux rejection, but by January 25, 2002 the price had fallen to \$14.90, and it would fall further.<sup>3</sup>

Soon, ImClone would face a Congressional inquiry,<sup>4</sup> an insider-trading investigation, and civil lawsuits, each

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<sup>2</sup>Erbitux is the trademark name for a drug referred to by ImClone as IMC-C225 (or C225). The generic name for Erbitux is Cetuximab.

<sup>3</sup>Dow Jones & Reuters, quotes available at <http://www.factiva.com/>. Also available at <http://table.finance.yahoo.com/k?s=imcl&g=d>.

<sup>4</sup>On June 13 and October 10, 2002, hearings were held by the Subcommittee on Oversight and Investigation of the Committee on Energy and Commerce of the U.S. House of Representatives.

seeking to determine how the FDA could dismiss a drug seemingly assured of passage. Hindsight is 20-20, and to date nothing conclusive indicates ImClone's management was anything less than convinced they were working on the next miracle drug. Clearly, however, somewhere in the process, someone dropped the ball.

Bringing new drugs to market implicates not only efforts by the company to secure the FDA's approval, but also a simultaneous effort to make investors, and consumers, aware of the progress of research and development. The valuation of biotechnology companies is largely based upon speculation about the future of the drugs in the company's pipeline, rather than current assets or sales. This type of speculation necessitates considerable reliance on the company itself to provide accurate and timely information on the development of products, and their progress towards the market.<sup>5</sup> But the biotechnology industry also relies heavily on secrecy. When hundreds of millions of dollars are needed to bring a successful drug to market, companies must take every precaution to ensure proprietary information does not leak to competitors. There is, therefore, an inherent tension that exists between the market's need-to-know, and a company's need for confidentiality. Closely connected with this tension are two administrative agencies: the FDA and the Securities and Exchange Commission. The FDA is charged with reviewing company applications to ensure drugs that reach the market are safe and effective. Because of the potential sensitivity of the information the FDA must review, Congress, and the agency itself, have limited what the agency may disclose to the public concerning the substance of applications.<sup>6</sup> By contrast, the SEC is responsible for ensuring that information that reaches the investing public is as accurate as possible. The SEC's regulations mandate that company disclosures must be accurate and complete, enabling investors to accurately value companies. But in the context of drug development, the SEC does not require, nor could it, disclosure of all the information received by the FDA.

The result is a regulatory quagmire: the FDA has the information necessary for investors to make informed

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<sup>5</sup>See Geeta Anand & Chris Adams, *ImClone Incident Spurs Demands For Greater Disclosure From FDA*, Wall St. J., Jan. 25, 2002, at A14, quoting Steven Harr biotechnology analyst at Robertson Stephens.

<sup>6</sup>See FDA's Authority to Monitor and Disclose Information, *infra* at page 26.

decisions, but is not permitted to disclose that information; the SEC is responsible for policing disclosures, often does not have access to the information necessary to do so.

In the case of ImClone, officials at the FDA were aware of the potential for company disclosures to mislead investors well before the issuance of the RTF, but took no action to remedy the problems, while the SEC only became aware of the problems after the damage was done. The intent here is not to point fingers. Much blame has fallen on ImClone's co-founder and former CEO, Sam Waksal. Dr. Waksal pleaded guilty last October to numerous counts of insider trading in the days before the Erbitux rejection,<sup>7</sup> and several stories have surfaced of numerous prior indiscretions committed by Waksal in the scientific community.<sup>8</sup> Despite the press given to Waksal's actions – and to alleged insider trading of Waksal's family and friends (most notably, Martha Stewart) – insider trading will be addressed only tangentially, in the context of what circumstances made such trades possible. Rather, the paper seeks to determine where the process of drug development and marketing – and the concomitant regulatory oversight – broke down, and what can be done to improve it. Part II discusses the FDA approval process for biologics such as Erbitux, the content of the Erbitux application, and the FDA's grounds for rejecting it. In Parts III and IV an attempt is made to determine whether either FDA or SEC had the authority and the opportunity, at the time, to take action to minimize the shock to the market of the Erbitux rejection. Finally, Part V looks at recent changes to the drug approval process, tries to determine how FDA and SEC might, separately or in tandem, work to avoid similar debacles in the future, and considers the future of ImClone and Erbitux. It is important to remember that, although the focus of the paper is on the development and rejection of Erbitux, the general scenario occurs daily as pharmaceutical and biotechnology companies work to bring drugs to market successfully.

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<sup>7</sup>Jerry Markon and Geeta Anand, Waksal Pleads Guilty as U.S. Widens Probe, Wall St. J., Oct. 16, 2002, at C1.

<sup>8</sup>See *infra* Note 239 at page 60.

## The Hype and the Big Deal

ImClone was not simply tooting its own horn when it lauded Erbitux as the best thing since sliced bread; the company was aided by numerous media outlets that picked up and dispersed the story of the cancer wonder drug. In a piece of prophetic irony, just two days before the FDA issued its RTF letter, the L.A. Times proclaimed “Erbitux . . . is set to make one of the biggest splashes of 2002.”<sup>9</sup> Several stories highlighted the results of ImClone’s registration study that FDA later rejected.<sup>10</sup> In an article about up-and-coming cancer therapies, Time Magazine reported that the study “showed that the drug could dramatically boost the effectiveness of standard colorectal-cancer chemotherapy, shrinking tumors in more than a fifth of otherwise hopeless cases.”<sup>11</sup> Business Week quoted an investor analyst who stated that the results announced by ImClone “substantiate our belief that C225 [Erbitux] could be a blockbuster, with potential for \$1 billion in annual sales.”<sup>12</sup> The magazine also ran a cover story on Erbitux in which it noted that the results of the registration study were “unusually high in such sick patients” and that “the official nod” was expected in early 2002.<sup>13</sup>

The hype was not baseless; in addition to reported trial results, Erbitux is credited with the recovery of several cancer patients in compassionate use programs.<sup>14</sup> Shannon Kellum of Florida had two tumors, one the size of a grapefruit and the other the size of an orange, that shrunk by 80 percent after she began treatment with Erbitux, and were eventually removed surgically.<sup>15</sup> Marilyn Caplan of New York had lung cancer that spread to her liver and brain. In 1999 she began taking Erbitux, and her cancer went away.<sup>16</sup>

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<sup>9</sup>Toni Clark, Biotech Industry Gaining Maturity Trends: There have been growing pains, but leaders have gained from their challenges, setbacks and failures, L.A. Times, Dec. 26, 2001, at C3.

<sup>10</sup>A “registration study” is a clinical trial used to seek FDA marketing approval.

<sup>11</sup>Michael D. Lemonick, et al., New Hope For Cancer, Time Magazine, May 28, 2001, at 62.

<sup>12</sup>Gene G. Marcial, ImClone May Have a Cancer Blockbuster, Business Week, June 11, 2001, at 163, quoting Cory Kasimov, analyst for Gruntal.

<sup>13</sup>Catherine Arnst, The Birth of a Cancer Drug, Business Week, July 30, 2001, at 46.

<sup>14</sup>Compassionate gives permits patients with no other options access to experimental therapies in some circumstances.

<sup>15</sup>*Id.*; Ron Winslow and Geeta Anand, *Laboratory Mixup: A Novel Cancer Drug, A Big Biotech Deal, And Now a Bitter Feud*, Wall St. J., Feb. 7, 2002, at A1 citing report of May 2000 ASCO conference.

<sup>16</sup>Geeta Anand, *Why ImClone’s Cancer Drug Seems So Promising*, Wall St. J., Feb. 27, 2002, at B1.

Others had similarly remarkable results.<sup>17</sup>

These types of responses no doubt contributed to Bristol-Myers Squibb's (BMS) willingness to enter into a \$2 billion agreement with ImClone in September, 2001. BMS agreed to purchase 19.9 percent of ImClone's stock in a \$1 billion tender offer at approximately a 75 percent premium over the market price at the time of the announcement.<sup>18</sup> BMS also agreed to another \$1 billion in milestone payments connected to Erbitux development and commercialization.<sup>19</sup> Internal BMS communications do reveal concerns about the Erbitux BLA, and especially about ImClone's assessment of the results of the primary registration study, which BMS officials considered optimistic.<sup>20</sup> Ironically, many of the concerns, would later be expressed by the FDA in rejecting the Erbitux application. At the time, however, they were not enough to deter BMS from making the deal.<sup>21</sup>

It was against this backdrop of glowing publicity and a billion dollars in new financing that ImClone submitted Erbitux to the FDA for marketing approval.

## Part II: Erbitux and the FDA

### The FDA Drug Approval Process in a Nutshell

The FDA approval process for new drugs, including biologics such as Erbitux, begins with the filing of an investigational new drug (IND) application seeking permission to conduct clinical trials on human subjects.<sup>22</sup>

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<sup>17</sup>*Id.* See also Catherine Arnst, *supra* Note 13.

<sup>18</sup>*An Inquiry Into the ImClone Cancer-Drug Affair: Hearings Before the Subcommittee on Oversight and Investigations of the Committee on Energy and Commerce, House of Representatives*, 107<sup>th</sup> Cong. (June 13 and October 10, 2002) (hereinafter *Hearings*) at 44 (Preliminary Committee Staff Report) available at <http://energycommerce.house.gov/107/hearings/06132002Hearing587/hearing.htm>.

<sup>19</sup>*Id.*

<sup>20</sup>See What Really Went Wrong? *infra* at Page 53-54.

<sup>21</sup>*Hearings*, *supra* Note 18 at 44-45.

<sup>22</sup>Although drugs and biologics are approved under authority of different statutory sections – 21 U.S.C. 355(b)(1) and 42 U.S.C. 262, respectively – the FDA Modernization Act of 1997 directs FDA to “minimize differences in review and approval”

Prior to filing a, however, a new chemical entity (NCE) will undergo years of laboratory and preclinical research to determine, among many other things, what it does, and how it does it. Among the purposes of the IND application are to ensure the safety of patients in future clinical trials, and “ensure the appropriateness and scientific design of studies under the IND so that the IND review process may efficiently anticipate and prevent problems which might arise” in later review,” and both of these concerns are taken into account in deciding whether to permit clinical trials to proceed.<sup>23</sup> At this stage, however, the agency’s primary responsibility is to protect the safety of human subjects, and review of the quality of scientific evaluation of drugs is focused in Phase II and III clinical trials.<sup>24</sup>

At the time of the Erbitux application, BLAs were reviewed by the FDA’s Center for Biologics Evaluation and Research (CBER). Ordinarily, a new drug must pass through three clinical trial phases before it may be submitted for marketing approval: Phase I clinical trials seek to determine the safety of the drug when administered to (usually healthy) volunteers; Phase II involves small trials to determine the efficacy of the drug in patients with the target disease; and finally, Phase III requires well controlled trials of several hundred, or even several thousand patients, to collect further pharmacological and toxicological data, as well as detect adverse reactions and potential interactions with other medications.<sup>25</sup> FDA has, however, approved biological products “based on single, multicenter studies with strong results,” under regulations for expedited approval.<sup>26</sup> These regulations were codified, with some modification, when Congress enacted the FDA Modernization Act of 1997 (Modernization Act).<sup>27</sup>

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(section 123(f)), and for purposes of this paper the process is effectively identical. Consequently, discussion of the “drug” approval process applies to biologics unless otherwise specified.

<sup>23</sup>Hutt, Peter Barton, and Richard A. Merrill. Food and Drug Law: Cases and Materials (2 ed.). The Foundation Press, Inc. (New York, 1991). Pg. 515

<sup>24</sup>Hutt and Merrill, pg. 515, note 3 at 517.

<sup>25</sup>Hutt and Merrill, pg. 516.

<sup>26</sup>Food and Drug Administration, Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (hereinafter “Providing Clinical Evidence of Effectiveness”) 4, (May 1998).

<sup>27</sup>P.L. 105-115. See also Food and Drug Administration, Guidance for Industry: Fast Track Drug Development Programs – Designation, Development, and Application Review (hereinafter “Fast Track Guidance”), (1998) at 1; ImClone Systems, Inc., Form 10-K 18 (2001).



Among other things, section 506 of the Modernization Act sets out requirements for “fast track” designation, and accelerated approval of drugs and biologics.<sup>28</sup> Fast track designation is available for a product “intended for the treatment of a serious or life-threatening condition [that] demonstrates the potential to address unmet medical needs for such a condition.”<sup>29</sup> In reviewing an application for fast-track designation the burden is on the applicant to meet these requirements, however FDA relies on summaries of data *provided by the applicant* in evaluating the drug’s potential.<sup>30</sup> This means FDA will not undertake an independent review of the data in making a fast-track designation. The fast-track process emphasizes “the critical nature of close early communication between the [FDA] and a sponsor,” including “efforts by the Agency and sponsor to reach early agreement on the design of the major clinical efficacy studies that will be needed to support approval.”<sup>31</sup> In addition, fast-track designation seeks to further expedite the review process by permitting the applicant to submit a BLA (or NDA for drugs) on a rolling basis, and authorizing – but not requiring – FDA to begin review of an application prior to its completion.<sup>32</sup>

Products granted fast track designation may also be approved on an accelerated basis under section 506(b).<sup>33</sup> The accelerated approval process permits approval of a license application “upon a determination that the product has an effect on a clinical endpoint *or on a surrogate endpoint that is reasonably likely to predict clinical benefit*.”<sup>34</sup> With respect to cancer, prior to the Modernization Act “FDA considered evidence of partial tumor shrinkage . . . insufficient by itself to warrant approval.”<sup>35</sup> Since February 19, 1998, however, the FDA has reversed course, and now considers products for accelerated approval based upon evidence of tumor shrinkage.<sup>36</sup> The Modernization Act also makes a significant change to the traditional FDA approval process

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<sup>28</sup>21 U.S.C. 506. See also Food and Drug Administration, Fast Track Guidance, *supra* Note 27 at 1.

<sup>29</sup>21 U.S.C. 506(a)(1) (1997).

<sup>30</sup>Food and Drug Administration, Fast Track Guidance, *supra* Note 27 at 7.

<sup>31</sup>Food and Drug Administration, Fast Track Guidance, *supra* Note 27 at 1. See also *Hearings*, *supra* Note 18 at 246.

<sup>32</sup>21 U.S.C. 506(c) (1997).

<sup>33</sup>21 U.S.C. 506(b) (1997).

<sup>34</sup>21 U.S.C. 506(b)(1) (1997) (emphasis added). See also *Hearings*, *supra* Note 18 at 246.

<sup>35</sup>ImClone Systems, Inc., Form 10-K 18 (2001).

<sup>36</sup>*Id.*

by amending the definition of “substantial evidence” in the Food, Drug, and Cosmetic Act (FDCA) from requiring evidence “from adequate and well controlled investigations” to permitting evidence of effectiveness to be established “with data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after the investigation), if the FDA determines, based on relevant science, that such data are sufficient.”<sup>37</sup> These provisions give the agency considerable flexibility in determining the extent and manner of information necessary to support a license application.

Nonetheless, fast-track products are still expected to undergo rigorous and sound scientific review.<sup>38</sup> The standards applicable to clinical trials are set forth at 21 C.F.R. 314.126. This section defines the purpose of clinical investigations as “distinguish[ing] the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation.”<sup>39</sup> To this end, the rule requires “the study report should provide sufficient details of study design, conduct, and analysis to allow critical evaluation and a determination of whether the characteristics of an adequate and well-controlled study are present.”<sup>40</sup> Part b of the rule lists characteristics of well-controlled studies; these include: a protocol with clear objectives and a method of analysis that “permits a valid comparison with a control to provide a quantitative assessment of drug effect;” adequate measures taken to properly select patients, and assign them to treatment or control groups; and steps taken to minimize bias at each stage, from patient enrollment to data analysis.<sup>41</sup> Several methods of “control” are recognized, including comparison of the experimental drug with known therapy – “active treatment control” – “where the condition treated is such that administration of placebo or no treatment would be contrary to the interest of the patient.”<sup>42</sup> In the case of active treatment control, the rule notes that “the report of the study should assess the ability of the study to have detected a

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<sup>37</sup>Jennifer Kulynych, *Will FDA Relinquish the “Gold Standard” for New Drug Approval? Redefining “Substantial Evidence” in the FDA Modernization Act of 1997*, 54 Food & Drug L.J. 127, 136 and 146 (1999).

<sup>38</sup>Food & Drug Admin., The FDA Modernization Act of 1997, FDA Backgrounder (Nov. 21, 1997); *Hearings*, *supra* Note 18 at 12 (Statement of Rep. Diana Degette, Member, House Comm. On Energy and Commerce).

<sup>39</sup>21 C.F.R. 314.126(a). *See also* Kulynych, *supra* Note 37 at 129.

<sup>40</sup>21 C.F.R. 314.126.

<sup>41</sup>21 C.F.R. 314.126(b).

<sup>42</sup>*Id.*

difference between treatments.”<sup>43</sup> Studies for accelerated approval often utilize active treatment control by looking at the experimental drug as a single-agent in patients having failed existing therapies.<sup>44</sup>

Pursuant to the Modernization Act, FDA has issued a guidance concerning the evidentiary requirements for demonstrating the effectiveness of drugs and biologics.<sup>45</sup> The guidance points out that more than one clinical trial is usually required because of “the need for *independent substantiation* of experimental results.”<sup>46</sup> In particular, multiple trials reduces the risk from systematic bias, random chance, site or investigator specific factors, and the occasional fraud, “by providing consistency across more than one study.”<sup>47</sup> Approval for a new drug – as opposed to a new use for an already approved drug – based on a single study “will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease . . . and confirmation of the result in a second trial would be practically or ethically impossible.”<sup>48</sup> As mentioned earlier, however, since 1998 the FDA has considered cancer products for approval based upon tumor shrinkage. The guidance notes that chances for approval are increased where a study has certain characteristics. Large, multicenter studies carry greater weight where no site provides an unusually large fraction of patients, and no investigator or site is disproportionately responsible for observed results.<sup>49</sup> Results are also more credible where: there is consistency across study subsets – such as age, gender, race, prior therapy, and disease stage; the activity of the drug can be assessed alone and in combination, especially where results can be compared to each other, and to a placebo; and where the drug is shown to be effective against multiple clinical or surrogate endpoints.<sup>50</sup> Finally, the more statistically significant the results, the better.<sup>51</sup> Regardless of whether approval is based upon one or many studies, “[t]o demonstrate

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<sup>43</sup> *Id.*

<sup>44</sup> *Hearings*, *supra* Note 18 at 39 (Preliminary Committee Staff Report).

<sup>45</sup> Food and Drug Administration, Providing Clinical Evidence of Effectiveness, *supra* Note 26.

<sup>46</sup> *Id.* at 4 (emphasis in original).

<sup>47</sup> *Id.* at 4-5.

<sup>48</sup> *Id.* at 13.

<sup>49</sup> *Id.*

<sup>50</sup> *Id.* at 13-14.

<sup>51</sup> *Id.* at 115.

that a trial supporting an effectiveness claim is adequate and well-controlled, extensive documentation of trial planning, protocols, conduct, and data handling is usually submitted to the Agency.”<sup>52</sup> The guidance notes that access to primary data is important because “study reports do not always contain a complete, or entirely accurate, representation of study plans, conduct and outcomes.”<sup>53</sup>

Typically, journal article peer reviewers only have access to a limited data set and analyses, do not see the original protocol and amendments, may not know what happened to study subjects that investigators determined to be non-evaluable, and thus may lack sufficient information to detect critical omissions and problems.<sup>54</sup>

## The Chemistry of Erbitux and its Biologics License Application

ImClone’s highly touted cancer drug, Erbitux, was created in the early 1980’s by Dr. John Mendelsohn, who joined ImClone’s board after the company acquired rights to the drug.<sup>55</sup> It is an epidermal growth factor receptor (EGFR) antagonist,<sup>56</sup> intended to prevent the binding of Epidermal Growth Factor (EGF) to EGFR, and thereby prevent cell proliferation, and inhibit cell survival.<sup>57</sup> In English, this means Erbitux acts something like those little plastic child-proof devices for wall outlets that plug into an electrical socket,

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<sup>52</sup>*Id.* at 16.

<sup>53</sup>*Id.* at 17.

<sup>55</sup>*Report to House Committee on Energy and Commerce by Raymond B. Weiss, MD, FACP* (hereinafter *Report of Dr. Weiss*), available at <http://energycommerce.house.gov/107/hearings/06132002Hearing587/hearing.htm>. Note that although this testimony is part of the ImClone hearings, *see supra* Note 18, it is not part of the transcript as available on the House committee’s website.

<sup>56</sup>There is already one EGFR monoclonal antibody, trastuzumab (Herceptin), on the market for the treatment of breast cancer, and other biotechnology companies are pursuing similar products. *Report of Dr. Weiss, supra* Note 55.

<sup>57</sup>Press Release, ImClone Systems, Inc., ImClone Systems Incorporated Reports on Anti-Angiogenesis Data at American Association for Cancer Research Meeting (March 30, 1998), available at <http://www.imclone.com/news>; Ron Winslow and Geeta Anand, *Laboratory Mixup: A Novel Cancer Drug, A Big Biotech Deal, And Now a Bitter Feud*, Wall St. J., Feb. 7, 2002, at A1; *Report of Dr. Weiss, supra* Note 55. *See also* ImClone Systems, Inc., *Erbitux*, available at <http://www.imclone.com/imc-c225.html> (as of April 20, 2003).

but do not activate the socket as a normal plug would. Erbitux is the correct shape to interact with specific receptors (sockets) on the surface of cancer cells, but does not activate the cell in any way. The importance is not so much in what Erbitux does directly, but in what it prevents other proteins from doing. The receptors Erbitux binds to (EGFR) are normally the target of other proteins (EGF) that signal a cell to grow and divide. When Erbitux binds to these receptors, it prevents the other proteins from signaling the cell. Because cancers become more dangerous, and harder to fight, the more they spread, the idea is to fight the cancer by blocking the receptors, thereby reducing the speed of the cancer growth. The receptors Erbitux acts to block are often, but not always found on cancer cells, and before treating patients with the drug it is necessary to first screen them to determine if their cancer cells are EGFR positive. These receptors are also found on ordinary body cells, but there are two critical differences: (1) research demonstrates normal cells are better at finding alternative signaling pathways to those blocked by Erbitux, allowing them to grow and divide normally; and (2) while normal cells may have about 10,000 of these receptors, cancer cells can have millions.<sup>58</sup> It is known that where these receptors are overexpressed in cancer cells, the cancer tends to proliferate and spread faster.<sup>59</sup>

ImClone filed an IND for Erbitux in 1994.<sup>60</sup> Since then, ImClone has tested Erbitux for safety and efficacy in preclinical and clinical trials for treatment of several types of cancer including head and neck cancer, renal cancer, and colorectal cancer.<sup>61</sup> In addition to the Phase II study which became the basis for the Erbitux BLA in 2001, the company conducted, and continues to conduct, numerous Phase II trials, and several Phase III trials.<sup>62</sup>

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<sup>58</sup>Lemonick et al., *supra* Note 11; Catherine Arnst, *supra* Note 13; ImClone Systems, Inc., *Erbitux*, *supra* Note 57. The range of EGFR expression varies among cancer types.

<sup>59</sup>*Report of Dr. Weiss*, *supra* Note 55.

<sup>60</sup>*Hearings*, *supra* Note 18 at 189 (Testimony of Patricia Keegan, Center for Biologics Evaluation and Research, Food and Drug Administration).

<sup>61</sup>ImClone Systems, Inc., *Erbitux*, *supra* Note 57.

<sup>62</sup>*Id.*; Press Release, ImClone Systems, Inc., ImClone Systems to Receive \$5 Million Milestone Payment from Partner, Merck KgaA, on ImClone Systems' Lead Cancer Therapeutic, C225 (March 9, 1999), *available at* <http://www.imclone.com/news>; Press Release, ImClone Systems, Inc., ImClone Systems to Initiate Second Phase III Pivotal Clinical Trial of C225 in Head and Neck Carcinoma (May 11, 1999), *available at* <http://www.imclone.com/news>.

The pivotal Phase II study relied on by ImClone in its BLA sought to determine the efficacy of Erbitux in combination with a standard chemotherapy drug, irinotecan, in refractory colorectal cancer patients.<sup>63</sup> “The whole scientific basis for clinical use of this new drug was that the combination of irinotecan and cetuximab [Erbitux] represented a potentially effective, third-line therapy for patients with metastatic [colorectal cancer] after failing prior 5-FU and irinotecan therapy.”<sup>64</sup> The company enlisted 139 patients, and measured the reduction in the size of their tumors over time – a surrogate endpoint for patient survival.<sup>65</sup> The trial, number 9923, was not originally intended as a registration study, however preliminary results encouraged ImClone’s management to approach FDA earlier than planned.<sup>66</sup> At an August 2000 meeting – after the study was underway, but before the results were fully analyzed – ImClone and FDA discussed the elements of an Erbitux BLA, and agreed on what the 9923 trial would need to establish for a license to be granted: (1) that patients had tumors that progressed despite prior treatment with irinotecan; (2) that at least 15 percent of patients responded to the combined regimen of Erbitux and irinotecan, with at least a 50 percent reduction in tumor size (known as a “partial response”); and (3) that the findings met statistical requirements.<sup>67</sup> The results of 9923 were initially announced to the 2001 annual meeting of the American Society of Clinical Oncology, and in a coinciding press release on May 12, 2001. Of 120 evaluable patients, ImClone reported that 27 patients (22.5%) had a partial response, with a median duration of response of 186 days.<sup>68</sup>

In the meantime, FDA granted Erbitux fast-track status on January 12, 2001.<sup>69</sup> As a condition of fast-

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<sup>63</sup>“Refractory” means the cancer progressed despite adequate prior treatment with the relevant drug, in this case irinotecan. Irinotecan is a chemotherapy drug also known as Camptosar, and CPT-11.

<sup>64</sup>*Report of Dr. Weiss, supra* Note 55; *Hearings, supra* Note 18 at 40 (Preliminary Committee Staff Report). Chemotherapy drug 5-fluorouracil (5-FU) was the only available drug for treatment of colorectal cancer between 1959 and 1996 when irinotecan was approved.

<sup>65</sup>*Report of Dr. Weiss, supra* Note 55. Of these 139 patients, 121 had progressive cancer after initial irinotecan treatment, but only 120 ended up in the final results. No information is available on what happened to the 121<sup>st</sup> patient.

<sup>66</sup>*Id.*

<sup>67</sup>Ron Winslow and Geeta Anand, *Laboratory Mixup: A Novel Cancer Drug, A Big Biotech Deal, And Now a Bitter Feud*, *supra* Note 15; *Report of Dr. Weiss, supra* Note 55.

<sup>68</sup>Press Release, ImClone Systems, Inc., ImClone Systems Announces Achievement of a 22.5 Percent Response Rate in its Phase II Clinical Study of IMC-C225 and Chemotherapy in Patients with Refractory Colorectal Cancer (May 12, 2001), *available at* <http://www.imclone.com/news>; *Report of Dr. Weiss, supra* Note 55.

<sup>69</sup>*Hearings, supra* Note 18 at 40 (Preliminary Committee Staff Report); Press Release, ImClone Systems, Inc., ImClone Systems Incorporated Receives fast track Designation for IMC-C225 From U.S. Food and Drug Administration (Feb. 1, 2001),

track designation, however, FDA required ImClone to conduct a small study of Erbitux as a single agent in colorectal cancer patients refractory for irinotecan.<sup>70</sup> In a January 19, 2001 letter to ImClone, FDA explained that the purpose of the single-agent study, along with other information requested, was to:

...exclude[ ] the possibility [at 95% confidence interval] that the response rate observed with the combination of irinotecan and Cetuximab [Erbitux] would not be observed with single agent Cetuximab at the dose and schedule proposed. You must provide evidence that continuation of a toxic agent (irinotecan) is necessary to achieve the desired clinical effect.<sup>71</sup>

ImClone enrolled 57 patients in study number 0141, intended to measure the efficacy of Erbitux as a single agent in individuals who failed prior treatment with three-drug chemotherapy regime (fluorouracil, leucovorin, and irinotecan). The trial was completed on October 12, 2001, and at the end of that month ImClone reported to FDA that six patients (10.5%) showed partial response.<sup>72</sup> The report of study 0141 marked the completion of the Erbitux BLA.<sup>73</sup>

## The RTF Letter and the Problems with ImClone's Science

It did not take FDA reviewers long to find problems with the Erbitux application, but one of the most troubling aspects of the ImClone case is the extent of the problems the agency uncovered, especially pertaining to the company's pivotal 9923 study. Despite monitoring by a contract research organization (PharmaNet),<sup>74</sup>

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available at <http://www.imclone.com/news>.

<sup>70</sup>*Hearings*, *supra* Note 18 at 40 (Preliminary Committee Staff Report, citing Jan. 19, 2001 letter from FDA to ImClone).

<sup>72</sup>*Id.* at 41 (Preliminary Committee Staff Report, quoting Jan. 19, 2001 letter from FDA to ImClone).

<sup>73</sup>Ron Winslow and Geeta Anand, *Laboratory Mixup: A Novel Cancer Drug, A Big Biotech Deal, And Now a Bitter Feud*, *supra* Note 15.

<sup>74</sup>*Report of Dr. Weiss*, *supra* Note 55.

FDA discovered numerous inconsistencies in the implementation of the study protocol, and a basic failure to provide adequate documentation to support the reported results. As discussed above, in the fast-track and accelerated approval processes the standard rules of drug approval are bent in an effort to get life-saving products to market.<sup>75</sup> Nonetheless, it is still necessary to demonstrate that the experimental drug is the cause of any observed results, and that all results are statistically significant.<sup>76</sup> In its RTF letter FDA concluded ImClone had failed on both counts.

ImClone's difficulties in demonstrating the effectiveness of Erbitux were created in part by its attempt to get the drug approved for use in conjunction with irinotecan. At the time, no drug had ever been approved through fast track based solely upon data in combination studies.<sup>77</sup> Harlan Waksal – who co-founded ImClone with his brother Sam and is the current CEO – testified that, based upon preclinical trials, ImClone concluded that Erbitux was ineffective as a treatment by itself, and therefore did not seek approval for the drug acting alone.<sup>78</sup> But analysis of the single-agent study revealed that although only 10.5 percent of patients responded – compared to a reported 22.5 percent in the combination study – the results from the two trials were not statistically distinguishable.<sup>79</sup> They failed, in other words, to meet the requirement set out in FDA's letter of January 19, 2001. Dr. Richard Pazdur of the FDA's Center for Drug Evaluation and Research (CDER) – which reviews licensing applications for conventional pharmaceutical drugs – noted that given the small size of the two studies “you had to have a zero percent [response] almost in the single

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<sup>75</sup> *Hearings*, *supra* Note 18 at 39 (Preliminary Committee Staff Report).

<sup>76</sup> *Id.* at 238.

<sup>77</sup> Ron Winslow and Geeta Anand, *Laboratory Mixup: A Novel Cancer Drug, A Big Biotech Deal, And Now a Bitter Feud*, *supra* Note 15; *Hearings*, *supra* Note 18 at 39 (Preliminary Committee Staff Report, quoting BMS Due Dilligence Findings of June 12, 2001). To my knowledge none have since.

<sup>78</sup> *Hearings*, *supra* Note 18 at 77 (Testimony of Harlan Waksal, CEO, ImClone Systems, Inc.).

<sup>79</sup> The Cancer Letter, *FDA Says ImClone Data Insufficient to Evaluate Colorectal Cancer Drug C225*, vol. 28, no. 1 (Jan. 4, 2002) (reporting the 95% confidence intervals for the combination and single-agent studies at 15.4%, 30.5%, and 4%, 21.5% respectively). See also Gardiner Harris, *ImClone Shares Fall Amid FDA Concerns*, Wall St. J., Jan. 8, 2002, at B14; *Hearings*, *supra* Note 18 at 209 (Testimony of Dr. Richard Pazdur, Center for Drug Evaluation and Research, Food and Drug Administration); Press Release, ImClone Systems, Inc., Data Presented on Study of ERBITUX™ (cetuximab) Combined with Docetaxel in Patients with Advanced Non-Small Cell Lung Cancer (May 19, 2002), available at <http://www.imclone.com/news>.



agent Erbitux study” to achieve a statistical difference in comparison with the 9923 study.<sup>80</sup> While the single-agent study supported ImClone’s contention that Erbitux is effective in fighting colorectal cancer, it undermined the company’s application for use in combination.

While comparing results from the two studies suggests Erbitux may work as well on its own as in combination, many of the problems the FDA found with the 9923 study raised more fundamental questions about whether Erbitux works at all. The agency noted several apparent violations of the study’s eligibility requirements, and especially the requirement that patients be refractory to irinotecan, making it difficult to determine which drug, Erbitux or irinotecan, caused the observed results. Dr. Pai-Scherf, the medical review officer for the Erbitux BLA, testified that he noticed early on in his review that key evidence documenting the refractory nature of patients was missing.<sup>81</sup> The doctor stated that necessary CAT scans were missing for at least 11 patients, and that the “clinical judgment” of researchers that these patients were refractory was not adequate to support licensure.<sup>82</sup> In addition to patients admitted even though they may not have been truly refractory, numerous patients were admitted that failed more basic criteria such as blood tests. Representatives for ImClone explained that exemptions from the enrollment criteria were issued in some cases where it was determined such exemptions would not affect the study results. Harlan Waksal acknowledged that ImClone failed in several instances to provide adequate documentation of patient eligibility, but he maintained that the major protocol deviation was admitting patients with abnormal liver tests where the doctor in charge determined there was no additional risk to the patient<sup>83</sup> However, independent oncology consultant, Dr. Raymond Weiss, testified that “[e]ligibility exemptions are *forbidden in all clinical trials* with which I have experience.”<sup>84</sup> Weiss acknowledged that eligibility errors do occur “5, 6, 8 percent of the

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<sup>80</sup> *Hearings, supra* Note 18 at 209 (Testimony of Dr. Richard Pazdur, Center for Drug Evaluation and Research, Food and Drug Administration).

<sup>81</sup> *Id.* at 210 (Testimony of Dr. Lee Pai-Scherf, Center for Biologics Evaluation and Research, Food and Drug Administration).

<sup>82</sup> *Id.*

<sup>83</sup> *Id.* at 72, 81 (Testimony of Harlan Waksal, CEO, ImClone Systems, Inc.).

<sup>84</sup> *Report of Dr. Weiss, supra* Note 55.

time,” but pointed out that the BMS review of the 9923 study, conducted in January 2002 concluded that 37 patients (30.8%) failed to meet at least one requirement of eligibility, and eight patients failed more than one requirement.<sup>85</sup> Fifteen of these 37 patients were given exemptions to enter the study, meaning researchers were aware of the patients’ ineligibility, but admitted them to the study anyway.<sup>86</sup> Dr. Weiss insisted that “[w]ithout carefully defining what category of patient is eligible for entry on such a study, any results from the trial will be subject to various biases and likely be meaningless.”<sup>87</sup>

Compounding the problem of patient ineligibility were inconsistencies in the dose and administration frequency of irinotecan during the trial. As with patient enrollment criteria, the exact method of administering drugs during a trial “must be defined and adhered to” in order to prevent bias in the results.<sup>88</sup> While the 9923 protocol required patients receive irinotecan in the same amount and frequency as prior to the study, BMS found at least 17 patients with major changes in irinotecan treatment after entering the study, including some dose increases.<sup>89</sup> Harlan Waksal maintained that the protocol “set out very clearly what should take place with Irinotecan treatment” in various circumstances, and that of the few cases where irinotecan dosage was increased, only one of the patients responded.”<sup>90</sup> But Dr. Weiss disagreed, contending that the protocol failed to provide instructions for modifying irinotecan dose or frequency in case of toxicity in a patient; “treating physician’s would thus make ad hoc decisions regarding this point, with multiple variations based on the physician’s best judgment.”<sup>91</sup> He argued that “[y]ou couldn’t separate the effect of increasing the dose of the one drug from the effect of the combination of the two drugs, either the Erbitux and/or the Irinotecan. When you are giving more of one drug than you had before, you are changing the results, and,

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<sup>85</sup> *Hearings*, *supra* Note 18 at 24 (Testimony of Dr. Raymond Weiss, Consultant in Oncology); *Report of Dr. Weiss*, *supra* Note 55.

<sup>86</sup> *Report of Dr. Weiss*, *supra* Note 55.

<sup>87</sup> *Id.*

<sup>88</sup> *Id.*

<sup>89</sup> *Id.*

<sup>90</sup> *Hearings*, *supra* Note 18 at 71 (Testimony of Harlan Waksal, CEO, ImClone Systems, Inc.).

<sup>91</sup> *Report of Dr. Weiss*, *supra* Note 55.

again, you make the results of the study subject to question.”<sup>92</sup>

Considering all the problems the FDA eventually expressed with Erbitux application, it is worth recalling that ImClone sought accelerated approval based upon a single study that already was complete. The 9923 study combined several features that were problematic, though not necessarily fatal, to its use as a registration study: (1) it was a combination study of Erbitux and irinotecan; (2) it studied tumor shrinkage as a surrogate for patient survival; and (3) only 120 patients were evaluated. Dr. Pazdur explained in his Congressional testimony that in seeking approval from CDER companies can request prior FDA approval of a study protocol, which is made binding on the agency through a Special Protocol Assessment.<sup>93</sup> CBER, however, has never used a Special Protocol Assessment for a biologic.<sup>94</sup> Ostensibly in an effort to explain why so many protocol violations occurred during the 9923 study, Harlan Waksal testified at the Congressional hearings that “the most important issue with this trial is that it was never initiated as a registration study, it was a Phase II study.”<sup>95</sup> But this simply begs the question: why was ImClone granted fast-track status in the first place?

## Part III: FDA Monitoring

The problems in the 9923 study protocol, and the data ImClone collected – or failed to collect – tell only one side of the story. On the other side are questions about why it took the FDA so long to confront the trial’s inadequacies, and why the agency allowed the positive publicity surrounding Erbitux to continue unchecked,

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<sup>92</sup> *Hearings*, *supra* Note 18 at 24 (Testimony of Dr. Raymond Weiss, Consultant in Oncology).

<sup>93</sup> *Hearings*, *supra* Note 18 at 39 footnote 1, 201 (Preliminary Committee Staff Report).

<sup>94</sup> *Id.*

<sup>95</sup> *Hearings*, *supra* Note 18 at 82 (Testimony of Harlan Waksal, CEO, ImClone Systems, Inc.).

even after it became aware of these problems. W.J. “Billy” Tauzin, the chairman of the House committee investigating the ImClone affair stated the problem this way:

[T]he leadership of [Imclone] had total control over what information would be released to the public, about its own studies and about the quality of this new product and about its potential since under our rules FDA is prohibited and restricted under Federal law from talking about such proprietary information. So we have a process whereby FDA is being restricted on what it can say about the clinical studies and about what is happening with this drug, while the company can go out and hype it and take advantage of it financially, while at the same time, according to our investigation, recognizing all the while that its studies were flawed and there were problems with the FDA approval process.<sup>96</sup>

These sentiments were echoed by other members of the committee who expressed concern that much of the damage created by the investor reaction to the Erbitux RTF letter could have been avoided if problems were identified earlier, and important information was relayed to the public where necessary.

## **Early Warning Signs**

Though the FDA remained in contact with ImClone as the company worked to complete the its BLA, the agency was not actively reviewing information as it was submitted by the company. But there were two points at which it is arguable the FDA should have taken steps to ensure accurate information reached the public. The first was in August of 2000, when the agency first reviewed the 9923 protocol. The second was in November and early December, 2001, when the agency was reviewing the Erbitux application.

## Problems with the Protocol

Evidence presented at the Congressional hearings made clear that the FDA had concerns about the 9923 trial as early as August 2000, when it first met with ImClone officials to discuss Erbitux licensing. In a pre-meeting to its scheduled August 2000 conference with ImClone, the primary FDA medical review officer expressed reservations about the 9923 study. Specifically, she was concerned that the proposed overall response rate target of 15 percent was not meaningful in a combination study, and that the study did not meet accelerated approval criteria and fast track criteria.<sup>97</sup> Further problems were pointed out during the congressional hearings by witnesses who reviewed the protocol after the fact. Dr. Weiss testified that the FDA should have told ImClone that specifications for giving Irinotecan were inadequate; an oversight that certainly contributed to the numerous inconsistencies noted in the RTF letter.<sup>98</sup> Dr. Pazdur added that the Erbitux development plan relied too heavily on preclinical activity in animal models.<sup>99</sup> “[T]o conduct a whole development plan and a sole development plan on an animal model is a very risky venture.”<sup>100</sup>

Nevertheless, the medical review officer was overruled by the head of CBER, Dr. Patricia Keegan, whose decision was based “on her belief that she should be flexible for a promising drug meeting an unmet medical need, but was also based on representations that ImClone made about the special synergistic effect of Erbitux when used in combination with irinotecan.”<sup>101</sup> Dr. Keegan testified that “there were issues with the protocol that were problematic, but presented with the results of the study, we didn’t consider it [sic] to be a fatal flaw, but a protocol that didn’t answer every question necessary to review the drug for approval.”<sup>102</sup> The FDA sought to answer some of these questions by requiring ImClone to conduct the 0141 single-agent study,

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<sup>97</sup>*Id.* at 39, 197-198.

<sup>98</sup>*Id.* at 30.

<sup>99</sup>*Id.* at 192 (Testimony of Dr. Richard Pazdur, Center for Drug Evaluation and Research, Food and Drug Administration).

<sup>100</sup>*Id.*

<sup>101</sup>*Id.* at 40, 198.

<sup>102</sup>*Id.* at 208 (Testimony of Dr. Patricia Keegan, Center for Biologics Evaluation and Research, Food and Drug Administration).

but Dr. Keegan’s testimony does not explain why so many concerns remained undiscovered, or at least unaddressed, by the time the BLA was completed.

Ironically, despite all the problems the FDA found with the 9923 study, it failed to realize until *after* issuing the RTF letter that in reviewing the study it was relying on the wrong version of the study protocol. The FDA’s minutes of the August 2000 meeting with ImClone – which were sent to the company for review - describe the 9923 protocol (Version 1.0) as requiring that enrolled patients “demonstrated progression of disease after completing a minimum of two courses of a regimen containing irinotecan.”<sup>103</sup> The same version of the protocol was described in the letter from the agency to ImClone pursuant to the grant of fast-track designation in January of 2001.<sup>104</sup> However, the protocol actually used in the study (Version 2.0) required only that a patient “has documented stable disease (must have received a minimum of 12 weeks of irinotecan therapy) or *progressive disease at any time after receiving an irinotecan-containing regimen*.”<sup>105</sup> The second version of the protocol effectively loosened the patient eligibility requirements because no minimum amount or duration of irinotecan therapy was required.<sup>106</sup>

At the Congressional hearing, ImClone officials defended the 9923 protocol, arguing that the problems with the study arose from improper execution, and failure to collect the necessary documentation, not from flaws in the study design.<sup>107</sup> Dr. Harlan Waksal testified that the protocol changes from Version 1.0 to 2.0 were “minor,” and that FDA was presented with the amended protocol “well before August 2000.”<sup>108</sup> The eligibility criteria were altered, he explained, because the “[m]edical practice doesn’t allow doctors to

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<sup>103</sup> *Id.* at 39-40 (Preliminary Committee Staff Report, internal quotes omitted), 89-90.

<sup>104</sup> *Id.* at 40 (Preliminary Committee Staff Report).

<sup>105</sup> *Id.* (internal quotes omitted, emphasis supplied in Staff Report).

<sup>106</sup> *Report of Dr. Weiss, supra* Note 55.

<sup>107</sup> *Hearings, supra* Note 18 at 278 (Testimony of Harlan Waksal, CEO, ImClone Systems, Inc.).

<sup>108</sup> *Id.* at 70-71 (Testimony of Harlan Waksal, CEO, ImClone Systems, Inc.).

continue patients on a drug if they have new lesions or progression. So the doctors, in conjunction with the company, made a modification to the protocol to allow patients who were failing the drug to be on the protocol.”<sup>109</sup> Though this may help explain variations in the time to refractory status of some patients, it raises the equally troubling question of whether continuing patients on irinotecan, even in combination with Erbitux, was ethical. At the hearing Dr. Pazdur stated that continuing treatment, with a toxic drug such as irinotecan, after patients failed initial therapy “violates every principle that I know of in medical oncology.”<sup>110</sup> By contrast, ImClone officials conveyed to FDA their belief that it would be unethical to study Erbitux as a single agent when preclinical data suggested it would be ineffectual.<sup>111</sup> Regardless of where the truth lies between the testimony of the FDA and ImClone officials, it is clear that a serious miscommunication occurred with respect to the version of the study protocol actually being used. More disturbing still is the prospect that a drug could be approved without FDA ever realizing it relied on the wrong protocol.

## **Deficiencies in the Data**

Despite early questions about the protocol, Dr. Keegan pointed out that, at the time of the August 2000 meeting, FDA was still relying on the company’s representation of the 9923 study results, and it was not until October 2001, when it received the clinical data for studies 9923 and 0141, that the agency realized flaws in the conduct of the study made the results problematic.<sup>112</sup> Assuming, for the sake of argument, that the protocol was not fatally flawed, this still does not explain the agency’s silence in those final two months

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<sup>109</sup>*Id.* at 77.

<sup>110</sup>*Id.* at 192 (Testimony of Dr. Richard Pazdur, Center for Drug Evaluation and Research, Food and Drug Administration).

<sup>111</sup>*Id.* at 199, 209.

<sup>112</sup>*Id.* at 207-208 (Testimony of Dr. Patricia Keegan, Center for Biologics Evaluation and Research, Food and Drug Administration), 41 (Preliminary Committee Staff Report).

when damage might have been mitigated.

As noted earlier, FDA reviewers realized soon after consideration of the completed BLA began in November, 2001, that the clinical research was “severely deficient and could not meet the legal requirement of an adequate and well-controlled clinical trial.”<sup>113</sup> But while the agency was aware that ImClone had announced the results of the study, and that those results were receiving considerable media attention, it did not suggest that the company retract, or qualify its earlier statements about the study. By November 30, the reviewers had decided to recommend that the agency refuse the Erbitux application, but this was not mentioned to the company during its December 4 meeting with the agency, nor was it suggested that the company make clear to investors that an RTF letter remained a possibility. Both Dr. Lilly Lee, who represented ImClone during the meeting, and George Mills of CBER, testified that the possibility of an RTF letter was discussed as one of several possible outcomes of the agency’s BLA review, but that Dr. Mills gave no indication that an RTF letter was not only likely, but almost inevitable.<sup>114</sup> Dr. Mills explained that he was only “halfway through the filing assessment,” and since the final decision had not been made he felt it was inappropriate to discuss internal agency communications with the company.<sup>115</sup> Even accepting that Dr. Mills’ caution was warranted, the FDA might still have informed the company when it came to a final decision to issue an RTF letter the very next day. Instead, the company was not notified of the decision until December 28, more than three weeks later. This created ample time for the information to leak, facilitating insider trading.<sup>116</sup>

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<sup>113</sup>*Id.* at 41-42 (Preliminary Committee Staff Report).

<sup>114</sup>*Id.* at 42 (Preliminary Committee Staff Report), 68 (Testimony of Dr. Lilly Lee, Vice President, Regulatory Affairs, ImClone Systems, Inc.), 203-204 (Testimony of Dr. George Mills, Center for Biologics Evaluation and Research, Food and Drug Administration).

<sup>115</sup>*Id.* at 204, 206 (Testimony of Dr. George Mills, Center for Biologics Evaluation and Research, Food and Drug Administration).

<sup>116</sup>*Id.* at 42 (Preliminary Committee Staff Report).



## FDA's Authority to Monitor and Disclose Information

There are three avenues by which information available to the FDA might theoretically reach investors. The most direct route is for the FDA to simply issue a press release providing any information necessary to protect the public. Alternatively, members of the public could seek to obtain information from the agency in order to better evaluate a drug's prospects. Finally, as discussed in Part IV, the FDA could share information with the SEC to help that agency take action to ensure a company's public disclosures are complete and accurate. In each case, however, the FDA is severely limited in its ability to disclose pertinent information.

Section 301(b) of the Public Health Service Act, 42 U.S.C. 242o gives FDA the authority to issue information "related to public health, in the form of publications or otherwise, for the use of the public . . . ." Nonetheless, FDA could not simply issue a press release to provide the world with evidence of the flaws in the Erbitux application. The FDA's own regulations largely prevent it from voluntarily disclosing to the public information contained in a BLA, except where the drug's sponsor consents. Regulation 21 CFR 601.51 states that, even when the existence of a BLA is public knowledge, "no data or information contained in the file is available for public disclosure before such license is issued."<sup>117</sup> This includes data from "all studies and tests of a biological product on animals and humans and all studies and tests on the drug for identity, stability, purity, potency, and bioavailability."<sup>118</sup> The regulation does permit the agency to disclose "a summary of such selected portions of the safety and effectiveness data as are appropriate for public consideration of a specific pending issue, e.g., at an open session of a Food and Drug Administration advisory committee . . .," but this narrow exception would not likely encompass a purely prophylactic disclosure of the kind needed

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<sup>117</sup>21 C.F.R. 601.51

<sup>118</sup>21 C.F.R. 601.51(g).

to alleviate public misperceptions about the strength of a pending BLA.<sup>119</sup> Consequently, even if agency officials had thought to do so, their ability to warn the public directly of the problems with the Erbitux BLA was extremely limited.

Nor could the problem be resolved if investors or public interest groups simply requested information from the agency about pending BLAs. Although the D.C. Circuit has determined that 21 CFR 601.51 does not itself prevent the FDA from responding to a request under the Freedom of Information Act (FOIA), 5 U.S.C. 552,<sup>120</sup> the FOIA generally allows administrative agencies to refuse to disclose such information under an exception pertaining to “trade secrets and commercial or financial information obtained from a person and privileged or confidential.”<sup>121</sup> For purposes of public disclosure, the FDA defines “trade secret” and “confidential commercial information” at 21 CFR 20.61. This regulation adopts the distinction between these two terms drawn by the D.C. Circuit in *Public Citizen Health Research Group v. FDA* (1983),<sup>122</sup> which rejected the broader Restatement of Torts definition of “trade secret,” previously adopted by the FDA, in favor of a narrower meaning:

A trade secret may consist of any commercially valuable plan, formula, process, or device that is used for the making, preparing, compounding, or processing of trade commodities and that can be said to be the end product of either innovation or substantial effort. There must be a direct relationship between the trade secret and the productive process.<sup>123</sup>

By contrast, confidential commercial information “means valuable data or information which is used in one’s business and is of a type customarily held in strict confidence or regarded as privileged and not disclosed to any member of the public by the person to whom it belongs.”<sup>124</sup> In *Public Citizen Health Research*

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<sup>119</sup>21 C.F.R. 601.51(d)(1).

<sup>120</sup>*Campaign for Responsible Transplantation v. FDA*, 219 F. Supp. 2d 106, 115, fn. 10 (D.D.C. Sept. 3, 2002).

<sup>121</sup>80 Stat. 250 (1966)

<sup>122</sup>704 F.2d 1280 (D.C. Cir. April 15, 1983). An unrelated case by the same name is cited later, and in order to distinguish the cases the year of the respective decisions will be included when the cases are cited by name.

<sup>124</sup>21 C.F.R. 20.61(b) (1994).

*Group* (1983), the D.C. Circuit determined that information “instrumental in gaining marketing approval” is clearly commercial for purposes of the FOIA exception.<sup>125</sup> However, courts have had a more difficult time determining if such information is confidential. In order to be confidential, disclosure of requested information must be likely to either: (1) impair the Government’s ability to obtain necessary information in the future; or (2) cause substantial harm to the competitive position of the party from whom the information was obtained.<sup>126</sup> The first clause is generally inapplicable where the information must be submitted to the agency, as is the case for clinical trial information when seeking a BLA.<sup>127</sup> Applying the second clause, results vary depending on the circumstances. In general the D.C. Circuit has recognized the potential competitive harm that could result from disclosure of information in a license application:

Thus, a drug manufacturer which has submitted an NDA has a competitive interest in seeing that the information contained in its NDA is not prematurely released to the public. If a manufacturer’s competitor could obtain all the data in the manufacturer’s NDA, it could utilize them in its own NDA without incurring the time, labor, risk, and expense involved in developing them independently.<sup>128</sup>

The court has recognized exceptions to this rule, but never where the information pertained to recent clinical trials used to support a pending license application.<sup>129</sup> There is little doubt, therefore, that the clinical trial data in the Erbitux BLA constituted confidential commercial information that could not be disclosed under the FOIA.

Despite these constraints, FDA does have some authority to address perceived misbehavior by drug sponsors.

The agency has the authority, under 21 U.S.C. 336, to issue written notice to companies notifying them of

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<sup>125</sup> *Public Citizen Health Research Group*, 704 F.2d at 1290.

<sup>126</sup> *Public Citizen Health Research Group v. FDA*, 185 F.3d 898, 903 (Aug. 6, 1999) (no relationship to the 1983 case of the same name).

<sup>127</sup> *Public Citizen Health Research Group v. FDA*, 704 F.2d at 1291.

<sup>129</sup> See *Teich v. FDA*, 751 F.Supp. 243 (D.C.Cir. Nov. 27, 1990) (Exception (b)(4) of the FOIA not applicable to release of “final results” and protocol information for animal tests where several factors, including the age of the tests, weighed against any commercial harm to the company).

agency concerns, and instructing them to cease any offending activity.<sup>130</sup> If the company persists, FDA may take further action, including suspending review of a drug application.<sup>131</sup> Informal warnings do have their limits, however. FDA still has no authority to regulate statements made prior to the relevant product coming under review by the agency.<sup>132</sup> CBER Director Keegan testified that enforcement is also constrained by limits in resources and staff.<sup>133</sup> And of course before FDA can take action it must become aware of a violation. Dr. Keegan pointed out that “we are often hampered in the pre-marketing setting by . . . not having the facts and the raw data, and not being able to tell how far off the mark they are. . . .”<sup>134</sup> This was largely the case with respect to Erbitux prior to the agency initiating review of the application. Perhaps FDA should have recognized the inadequacy of the trial protocol in August 2000, but since it did not, it had no reason to take action against the company. The agency had no cause, at that time, to doubt the veracity or good faith of ImClone’s contentions about Erbitux efficacy. Nor were the company’s public disclosures such that the agency should have been concerned. As discussed in greater detail in Part IV, during the period before October 31, 2001, statements by ImClone concerning the results of the 9923 trial, and results from other trials, were typical of a biotechnology company, and in keeping with the information available to the agency. Consequently, there was probably not sufficient evidence of wrongdoing for FDA to take action prior to commencing review of the BLA.

Once the review began, however, and the problems with the data became readily apparent, the FDA arguably

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<sup>130</sup>Untitled letters and Warning letters are available under the Freedom of Information Act, and some are available on the FDA website, but no public announcement is made when they are issued. Examples of past FDA enforcement actions were supplied for the record at the hearing, however they provide limited insight into the ImClone situation because they all deal with efforts to revoke approval based upon false or misleading information provided to the *agency*, not to the public. *Hearings*, *supra* Note 18 at 243, 245 (Testimony of Dr. Lester Crawford, Deputy Director, Food and Drug Administration).

<sup>131</sup>*Hearings*, *supra* Note 18 at 231-232 (Testimony of Dr. Lester Crawford, Deputy Director, Food and Drug Administration).

<sup>132</sup>*Id.* at 247 (Testimony of Dr. Lester Crawford, Deputy Director, Food and Drug Administration).

<sup>133</sup>*Id.* at 194 (Testimony of Dr. Patricia Keegan, Center for Biologics Evaluation and Research, Food and Drug Administration).

<sup>134</sup>*Id.* at 202 (Testimony of Dr. Patricia Keegan, Center for Biologics Evaluation and Research, Food and Drug Administration).

had adequate cause to take some corrective measures. FDA officials certainly could have communicated their concerns to ImClone management, perhaps at the December 4 meeting, and recommended the company withdraw the application or otherwise caution investors of the agency's concerns. While acknowledging that the Center has the authority to do so, Dr. Keegan testified that CBER was not in the habit of notifying a company of an upcoming RTF letter, and that in her opinion such notification "might to some extent be considered coercive," though she did not explain why.<sup>135</sup> By contrast, Dr. Pazdur noted that CDER does sometimes choose to notify a company if an RTF letter is inevitable, and give the company the chance to withdraw.<sup>136</sup> But even if this information was conveyed to the company, there's no guarantee it would have done much to prevent insider trading and shareholder losses. As an alternative, when the agency first became aware of the problems with the 9923 study in November, the FDA could have chosen to issue a press release stating simply that its preliminary assessment of the Erbitux application raised concerns about the results previously disseminated by ImClone. Such a release need not provide any confidential information, and because the existence of the Erbitux BLA was well publicized by the company the announcement would not run afoul of any disclosure rules. The agency recently adopted this tactic when, on March 14, 2003, it issued a public warning about misrepresentations in a press release by SuperGen, Inc. concerning that company's cancer drug, Mitozytrex.<sup>137</sup> The announcements points to several inaccuracies, including that the company "exaggerates the efficacy of Mitozytrex and fails to include the significant risks associated with the use of the drug." The agency notes that SuperGen made statements suggesting its drug was superior to existing drugs, and warned that "[n]o data submitted by the company provided evidence that Mitozytrex is superior to existing marketed formulations of [competing drug]." A similar warning could have been issued in November 2001 to alert the public about the risks of relying on ImClone's analysis of the 9923 trial. The

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<sup>135</sup>*Id.* at 207 (Testimony of Dr. Patricia Keegan, Center for Biologics Evaluation and Research, Food and Drug Administration).

<sup>136</sup>*Id.* at 206 (Testimony of Dr. Richard Pazdur, Center for Drug Evaluation and Research, Food and Drug Administration).

<sup>137</sup>Food and Drug Administration, FDA Warns Public About Misrepresentations in Marketing Claims About Drug to Treat Cancer, FDA Talk Paper (March 14, 2003).

issuance of a preliminary opinion is not without risks. Announcements of this sort could cause a company's stock price to fluctuate wildly if used too often, and not phrased carefully. Nonetheless, the considerable problems found in the Erbitux BLA, combined with the equally considerable hype in the media, suggest this was a situation in which such a letter might have been warranted.

## Part IV: SEC Disclosure Rules

Although FDA did not take any direct enforcement action, many of the concerns conveyed to ImClone in the RTF were expressed in various prior communications with the company; unfortunately, they never reached the public.<sup>138</sup> Because the valuation of biotechnology companies is largely based upon speculation about the success of products not yet on the market, investors necessarily rely heavily on information provided by the company. Unfortunately, even to the extent FDA may be able to regulate disclosures once an application for marketing approval is filed – which we've seen is very limited – the agency has no authority to police disclosures up to that point. FDA may, however, choose to share its concerns with the SEC.

In this context, the distinction between “trade secret” and “confidential commercial information,” discussed in the previous section, is especially important. Under agency regulations, the FDA may disclose non-public information to other government agencies, while still maintaining the non-public nature of the information, if certain conditions are met.<sup>139</sup> While the regulations, in conjunction with section 331(j) of the FDCA,

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<sup>138</sup>Chris Adams, *ImClone, Bristol-Myers Mull Altering Pact*, Wall St. J., Feb. 11, 2002, at A12; *Report of Dr. Weiss, supra* Note 55.

<sup>139</sup>21 C.F.R. 20.80, 21 C.F.R. 20.85.

prohibit the agency from sharing trade secret information outside the Department, no such restriction limits the agency's ability to share confidential commercial information.<sup>140</sup> We've already seen that in the context of the FOIA, courts have characterized clinical trial protocols and data as commercial information, rather than trade secret information, suggesting FDA could have supplied SEC with concrete evidence concerning the problems with ImClone's 9923 trial.<sup>141</sup> But even if FDA chose not to disclose specifics, it could easily have expressed general concerns about ImClone's disclosures, and recommended an investigation. Dr. Crawford testified before Congress that according to FDA's Office of Chief Counsel, FDA and SEC are in daily communication, suggesting FDA could pass along information about possible false or misleading statements and rely on SEC for enforcement.<sup>142</sup>

Nonetheless, it may be that SEC's ability to police information like that contained in the ImClone press releases suffers from more fundamental problems. First, there is some concern that, even where SEC is made aware of possible problems, it may lack the resources, to say nothing of the scientific expertise, needed to evaluate the accuracy of many statements made by biotech companies; particularly pertaining to the importance of trial results. The biggest hurdle, however, may be that many of the statements made by ImClone simply did not constitute violations of the securities laws.

## Questions of Integrity

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<sup>140</sup>21 C.F.R. 20.85, 21 U.S.C. 331(j).

<sup>141</sup>It must be noted that prior to the D.C. Circuit's 1983 decision in *Public Citizen Health Research Group*, the FDA applied a much broader definition of "trade secret" that encompassed clinical trial information, and in that case the court explicitly stated that the definition it adopted only applied in the context of Exemption 4 of the FOIA (704 F.2d 1280, 1290 footnote 27). It is possible, therefore, that FDA could argue that 331(j) prohibits disclosure of clinical trial information under a broader definition of "trade secret;" however because the agency's definitions of "trade secret" and "commercial information" are found in the same Part of its regulations as the rules permitting disclosure to other agencies, this seems unlikely.

<sup>142</sup>*Hearings*, *supra* Note 18 at 231 (Testimony of Dr. Lester Crawford, Deputy Director, Food and Drug Administration).

The integrity of ImClone's disclosures, and more specifically those of its co-founder Sam Waksal, were increasingly questioned and scrutinized in the wake of the Erbitux rejection. Just days after receipt of the RTF letter, Sam Waksal sought to reassure investors that the issues in the RTF "all come out of the fact that we have great data and great results but we did not document properly to their satisfaction the train of thought that got us from point A to Z."<sup>143</sup> Despite evidence to the contrary, Waksal stated that independent reviews of the study results showed that "there is *concordance across the board*."<sup>144</sup> He claimed that "the crux of the FDA's refusal is that the company failed to provide documentation of the 'refractory' nature of patients enrolled in the pivotal-stage trial used to support the marketing application."<sup>145</sup> On January 4, however, The Cancer Letter reported that it had acquired a copy of the normally secret RTF letter, and that the letter "detailed a long list of concerns that the FDA had over Erbitux's application that go far beyond record-keeping errors" including failure to provide sufficient evidence of Erbitux activity.<sup>146</sup> The RTF also allegedly indicated that FDA had problems with the protocol for trial 9923 from the beginning, contrary to statements made by Waksal.<sup>147</sup> More questions were raised by the Congressional hearings where evidence was presented that ImClone and BMS sought to make disclosures following the RTF intentionally vague.<sup>148</sup> While these problems concern statements made after the Erbitux rejection, they do not bode well for the integrity of statements made earlier. The possibility that disclosures by ImClone may have violated SEC rules, and led to investor loss is troubling. Perhaps more troubling, however, is the extent to which much of what ImClone announced to the public would not qualify as false or misleading under current law. The primary difficulty seems to be that the SEC disclosure rules were not written with the biotechnology or pharmaceutical communities in mind. Over the course of several years, ImClone released information on a

<sup>143</sup>Rachel Zimmerman, *Cancer Treatment By ImClone, Bristol Hits FDA Hurdle*, Wall St. J., Jan. 2, 2002, at A8.

<sup>144</sup>*Report of Dr. Weiss*, *supra* Note 55. (quoting Sam Waksal, internal quotations omitted, emphasis supplied in testimony).

<sup>145</sup>*ImClone May Need New Erbitux Trials, Delaying Its Launch*, Wall St. J., Jan. 10, 2002, at B6.

<sup>146</sup>*The Cancer Letter*, vol. 28, no. 1, pg. 1-5. See also Gardiner Harris, *ImClone Shares Fall Amid FDA Concerns*, Wall St. J., Jan. 8, 2002, at B14. It's worth noting that whoever provided The Cancer Letter with a copy of the RTF violated federal law.

<sup>147</sup>Rachel Zimmerman, *Cancer Treatment By ImClone, Bristol Hits FDA Hurdle*, *supra* Note 143.

<sup>148</sup>Geeta Anand and Gardiner Harris, *ImClone, Bristol Had Discussed Vague Disclosures*, Wall St. J., June 14, 2002, at A3.



regular basis concerning the results and ongoing progress of its preclinical and clinical Erbitux trials. Often, this information included data involving the number of patients responding to treatment, and the extent of their response. Missing from these releases, however, are at least two important pieces of information. First, study protocols are not released, except in the most basic form, making it impossible for investors to determine the adequacy of controls in these studies. Second, no information about the statistical significance of study data is released, making it impossible to evaluate the scientific validity of the results. Compounding this problem is the frequent use of words such as “significant” to describe study results, but without any attempt to define what is “significant.”<sup>149</sup> ImClone is certainly not alone in these respects, which merely compounds the problem. Unable to evaluate the scientific merits of information provided by a company investigating a new drug, investors are flying blind.

## Scope of SEC Authority

False or misleading statements or omissions of material fact are actionable under SEC Rule 10b-5, 17 C.F.R. 240.10b-5, promulgated pursuant to section 10(b) of the Securities Exchange Act of 1934, 15 U.S.C. 78j(b).<sup>150</sup> Statements must be “false” at the time they were made, and more specifically, must have “no good faith, reasonable, objective basis.”<sup>151</sup> In addition to disclosures mandated by law, “voluntary disclosure of information that a reasonable investor would consider material must be complete and accurate.”<sup>152</sup> Omissions are only actionable if there was a duty to disclose the omitted information, usually because the information

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<sup>149</sup>See Press Release, ImClone Systems, Inc., ImClone Systems’ Lead Cancer Therapeutic, C225, Demonstrates Anti-Tumor Activity in Preclinical Models of Pancreatic Carcinoma (April 14, 1999), ImClone Systems and Collaborators Present Preclinical Data on Mechanism and Anti-Tumor Activity of Lead Cancer Therapeutic, IMC-C225, in Combination with Radiation (April 4, 2000), ImClone Systems Presents Preclinical Data on Anti-Tumor Activity of IMC-C225 in Combination with Chemotherapy in Colorectal Carcinoma (March 26, 2001) available at <http://www.imclone.com/news>.

<sup>150</sup>*In re Biogen Sec. Litig.*, 179 F.R.D. 25 (D. Mass. Sept. 4, 1997) at 36 citing *Shaw v. Digital Equipment Corp.*, 82 F.3d 1194, 1217 (1<sup>st</sup> Cir. 1996); *In re Synergen, Inc. Sec. Litig.*, 863 F. Supp. 1409, 1410 (D. Colo. Sept. 15, 1994).

<sup>151</sup>Fisher, 8 Mich. Telecomm. & Tech. L. Rev. 115 at 118

<sup>152</sup>*Backman v. Polaroid Corp.*, 910 F.2d 10, 13 (1<sup>st</sup> Cir. 1990) (internal quotes omitted).

was necessary to make other mandatory or voluntary disclosures not misleading.<sup>153</sup> Omissions are material if there is “a substantial likelihood the disclosure of the omitted fact would have been viewed by the reasonable investor as having significantly altered the ‘total mix’ of information available.”<sup>154</sup> It is not enough to demonstrate the company might not have believed what it said, rather the plaintiff must demonstrate that the company could not have believed what it said, and was therefore either knowing or reckless.<sup>155</sup> It is important to note that “[I]n the context of a Section 10(b) action ... [courts] must consider all of the allegations of the complaint in the aggregate,” rather than looking at isolated statements or omissions.<sup>156</sup>

During the months and years prior to the Erbitux rejection, ImClone repeatedly disclosed to the public, in press releases and SEC filings, the progress of Erbitux development and the ongoing efforts to acquire FDA approval.<sup>157</sup> In addition to rosy statements of the drug’s potential, the company made specific reference to numerous preclinical and clinical trials purporting to demonstrate the drug’s safety and efficacy. Even students of science and statistics could be excused for getting swept up in the seemingly promising results, and no doubt they contributed to the steady rise of ImClone’s stock price. Nonetheless, in its RTF letter the FDA noted a failure by ImClone to abide by standard scientific protocol in the design and implementation of the 9923 study, and in data analysis for that study. This illustrates quite clearly that the results of studies are meaningless if those studies are poorly executed, but in many situations – including ImClone’s, perhaps – the flaws behind the numbers are not discovered until well after the fact. There is clearly a need to ensure

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<sup>153</sup>*In re Synergen, Inc. Sec. Litig.*, 863 F. Supp. at 1418 citing *In re Time Warner, Inc. Sec. Litig.*, 9 F.3d 259, 267 (2d Cir. 1993).

<sup>154</sup>*Id.*, 863 F. Supp. at 1417 citing *Basic, Inc. v. Levinson*, 485 U.S. 224, 108 (1988), and *TSC Indus., Inc. v. Norhway, Inc.*, 426 U.S. 438, 96 (1976).

<sup>155</sup>*Virginia Bankshares, Inc. v. Sandberg*, 501 U.S. 1083 at 2760 (1991).

<sup>156</sup>*Walsingham v. Biocontrol Tech., Inc.*, 66 F.Supp. 2d 669, 676 (W.D.Pa. 1998) citing *Isquith v. Middle South Utilities, Inc.*, 847 F.2d 186, 189-90 (5<sup>th</sup> Cir. 1988), and *SEC v. C.R. Richmond & Co.*, 565 F.2d 1101, 1106-07 (9<sup>th</sup> Cir. 1977).

<sup>157</sup>ImClone’s 1999 and 2000 Annual Reports comment on the results of clinical trials, and the intention to seek marketing approval, but no data is disclosed, and discussions of commercialization are well qualified. Consequently, they will not be discussed.

that data and statistics are presented with sufficient supplementary information to put them in context, and adequately caution investors of uncertainties.

The experience of ImClone and other companies provide some insight into the scope and content of information necessary to make disclosures concerning drug development as informative as possible, while still protecting the proprietary information of the company. In a recent article, William Fisher notes three areas of disclosures that may create problems in the process of drug development: (1) statements about the chances of FDA approval; (2) disclosure of clinical test results; and (3) statements about communications with FDA before approval.<sup>158</sup> Each of these may give rise to civil liability, and SEC litigation.

### **Predictions of FDA Approval**

Companies are under no obligation to project the likelihood of FDA approval, but often do so anyway, ostensibly to keep shareholders informed, and probably to drum up anticipation in the market.<sup>159</sup> Congress and the courts have created a high threshold for establishing liability in the case of predictions of future events, such as FDA approval, where some precautions are taken by the company. In addition to the pre-existing burdens on plaintiff's in 10b-5 lawsuits, the Private Securities Litigation Reform Act (PSLRA) may broaden the protection for company disclosures. Fisher argues that, though not explicitly included in the PSLRA's definition of "forward-looking statement," projections of FDA approval "could certainly be phrased as an 'objective of management,' and could also be disclosed as an assumption underlying predicted future

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<sup>158</sup>Fisher, William O., "Key Disclosures Issues for Life Sciences Companies: FDA Product Approval, Clinical Test Results, and Government Inspections," 8 Mich. Telecomm. & Tech. L. Rev. 115 (2002), 116-117. Though Fisher does not discuss ImClone, much of this section borrows from his very insightful article. Fisher also deals with a fourth topic – "Disclosing and Commenting on Government Inspections, Investigations and Prosecutions – which is not implicated in the ImClone case.

<sup>159</sup>*Id.* at 117-118, footnote 4.

financial performance.”<sup>160</sup> In addition to requiring plaintiff’s to prove the company had “actual knowledge” that the prediction was false or misleading, the PSLRA further provides a statutory safe harbor from private actions where a qualifying forward looking statement is accompanied by “meaningful” cautionary language identifying important factors that could cause variations from the predicted result.<sup>161</sup> What constitutes “meaningful” cautionary language is still up in the air, but at least one court concluded that the statement that a company believed its FDA application was “on track for approval this year” was not actionable where accompanied by language indicating the uncertainties of the FDA approval process, and the possibility that approval may not be granted.<sup>162</sup> That case adopted the approach of *MedImmune*, decided prior to the PLSRA, in which the court stated that “while it is true that a ‘guarantee’ of approval of a product by a federal agency might be actionable, the key word is ‘guarantee.’”<sup>163</sup> In *MedImmune* the court – noting that the defendant qualified most references to FDA approval with “variations of the proviso ‘if and when approved by FDA’” – maintained that “[m]ere expressions of hope or expectation regarding future approval . . . are not actionable.”<sup>164</sup> The safe harbor does have limits, however, and Fisher cautions companies to consider disclosing any facts that could affect FDA approval, including the possibility that the company and the agency will have differing interpretations of clinical test results, and the potential for human error in the conduct and evaluation of trials that could alter future results.<sup>165</sup>

ImClone’s press releases carry with them a standard warning about forward looking statements, which states

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<sup>160</sup>*Id.* at 119, footnote 10.

<sup>161</sup>Cox, James D. et al. *Securities Regulation: Cases and Materials* (3d ed.). Aspen Law & Business (New York, 2001), at 74.

<sup>162</sup>*In re PLC Systems, Inc. Sec. Litig.*, 41 F. Supp. 2d 106, 117-118 (D. Mass. 1999) (pointing out that statements of possible FDA approval were qualified using words such as “believe” and “expect.”).

<sup>163</sup>*In re MedImmune, Inc. Sec. Litig.*, 873 F. Supp. 953 (D. Md. 1995) at 964 (internal citation omitted); *In re PLC Systems, Inc. Sec. Litig.*, 41 F. Supp. 2d at 118.

<sup>164</sup>*In re MedImmune, Inc. Sec. Litig.*, 873 F. Supp. at 964.

<sup>165</sup>Fisher, 8 Mich. Telecomm. & Tech. L. Rev. 115 at 123, and 126-127 citing *In re Cell Pathways, Inc. Sec. Litig.*, Fed. Sec. L. Rep. (CCH) P91,001 (E.D. Pa. June 20, 2000) (holding that cautionary language does not protect a forward looking statement where the plaintiffs “allege omission of the facts causing predictions to fail rather than attacking the predictions as affirmative misstatements”).

that “[a]ctual results may differ materially from those predicted in such forward-looking statements due to the risks and uncertainties inherent in the Company’s business . . .,” and mentions several non-inclusive factors affecting future results including “risks and uncertainties in obtaining and maintaining regulatory approval.”<sup>166</sup> Beginning with its May 22, 2000 press release, ImClone added a new warning to its Erbitux related disclosures:

Imclone Systems’ IMC-C225 [Erbitux] is an investigational drug currently being evaluated in clinical trials. The determination of the safety and effectiveness of this product is subject to evaluation by the U.S. Food and Drug Administration (FDA). FDA has not reviewed or determined that the information in IMC-C225 is sufficient for approval.<sup>167</sup>

Curiously, this warning only appeared in relevant press releases through the end of 2000, and only one of those releases – from November 8, 2000 – discussed the prospect of FDA licensing. The November release quotes Harlan Waksal, commenting on preliminary results from the 9923 study, as saying, “data are being prepared as expeditiously as possible for review by the U.S. Food and Drug Administration and we expect to submit a filing in the first half of 2001.”<sup>168</sup> The warning does not appear in a March 26, 2001 release in which Harlan Waksal was again quoted as saying the company was “preparing data from [9923 study] for a filing with the FDA in the first half of this year.”<sup>169</sup> Nor does it appear in the February 1, 2001 press release announcing that FDA had granted Erbitux fast-track designation, or in the June 28, 2001 and November 1, 2001 releases announcing, respectively, the initial filing and the completion of the Erbitux rolling BLA.<sup>170</sup> It

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<sup>166</sup>Press Releases, ImClone Systems, Inc., *available at* <http://www.imclone.com/news>.

<sup>168</sup>Press Release, ImClone Systems, Inc., ImClone Systems Announces Favorable Preliminary Results in Phase II Study of IMC-C225 and Irinotecan in Patients with Refractory Colorectal Carcinoma (Nov. 8, 2000), *available at* <http://www.imclone.com/news>.

<sup>169</sup>Press Release, ImClone Systems, Inc., ImClone Systems Presents Preclinical Data on Anti-Tumor Activity of IMC-C225 in Combination with Chemotherapy in Colorectal Carcinoma (March 26, 2001), *available at* <http://www.imclone.com/news>.

<sup>170</sup>Press Releases, ImClone Systems, Inc., ImClone Systems Incorporated Receives fast track Designation for IMC-C225 From U.S. Food and Drug Administration (Feb. 1, 2001), ImClone Systems Initiates Filing of Rolling Biologic License Application with the FDA for Approval of IMC-C225 to Treat Refractory Colorectal Cancer (June 28, 2001), ImClone Systems and Bristol-Myers Squibb Announce Completion of Rolling Biologics License Application Filing for ERBITUX, Formerly IMC-C225, to Treat Irinotecan-Refractory Colorectal Carcinoma (Nov. 1, 2001), *available at* <http://www.imclone.com/news>.

is not clear why the warning appeared for such a short period of time, though it may have been superfluous. None of ImClone's press statements contain anything resembling a "guarantee" of FDA approval, and the hazards of the regulatory approval process are mentioned in the company's standard warning on forward looking statements.

Similarly cautious language exists in ImClone's annual 10-K filings with SEC. In addition to noting the complexities of the FDA approval process, the company acknowledges that it "has limited experience in conducting and managing preclinical testing necessary to enter clinical trials required to obtain government approvals and has limited experience in conducting clinical trials," and therefore "the Company's competitors may succeed in obtaining FDA approval for products more rapidly than the Company, which could adversely affect the Company's ability to further develop and market its products."<sup>171</sup> The company is also careful to qualify statements concerning FDA approval, using language such as "when and if we receive . . . required regulatory approvals,"<sup>172</sup> and noting that "[t]here can be no assurance that we will receive regulatory approval for IMC-C225 [Erbixux] based on the results of our ongoing Phase II clinical trials or any of our other ongoing or anticipated IMC-C225 clinical trials."<sup>173</sup> In its 2001 10-K, ImClone does comment on its marketing intentions for Erbixux "[u]pon the receipt of regulatory approval," where cautionary language concerning the prospects for approval only appears later in the report.<sup>174</sup> There is no rule setting out the required proximity of cautionary language to forward looking statements, but it is possible a court could find such warnings inadequate where sufficiently removed from a material misrepresentation. In all likelihood, however, this is not such a case.

It seems, therefore, that ImClone maintained a reasonable degree of caution in making statements concerning the prospects of Erbixux approval. Although numerous reports outside the company predicted FDA would

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<sup>171</sup>ImClone Systems, Inc., Form 10-K 10-11, F-7 (March 1998), Form 10-K 14-15, F-7 (March 1999). Form 10-K 3, 14, F-7 (March 2000); Form 10-K 17-18, F-7 (March 2001).

<sup>172</sup>ImClone Systems, Inc., Form 10-K 1 (March 1999).

<sup>173</sup>ImClone Systems, Inc., Form 10-K 3 (March 2000).

<sup>174</sup>ImClone Systems, Inc., Form 10-K 1, 17-18, F-7 (March 2001).

grant a license, it is difficult to see how the company could be held liable on these grounds.

## **Revealing Results**

Risks associated with forward-looking statements exist for any publicly traded company, but biotechnology and pharmaceutical companies also have the more unusual problem of relying on trial data to support many of their disclosures. Difficulties created by differing interpretations of data are bad enough, but the problem is often compounded because companies may release preliminary results, before the study is even complete. ImClone revealed much of its preclinical and clinical trial results at the annual meetings of the American Association for Cancer Research, the American Society of Clinical Oncology, and the American Society for Therapeutic Radiology. These announcements were accompanied by company Press Releases, often including statements from company officials. The mix of raw data and interpretive statements in the ImClone disclosures exemplifies the typical problem life science companies face. To make such information accessible to the masses, companies may prefer to simply comment on results, without presenting data that could be misconstrued, or at least provide explanations to accompany the data. In doing so, however, the company risks making statements that could be misinterpreted, and render the disclosure misleading. Consequently, a company may decide to simply present the “hard” information to avoid the risk of making misleading statements. This, of course, renders the company subject to claims that insufficient context was provided to allow investors to accurately interpret the information.

The use of data is not necessarily problematic, however in a world seemingly run by opinion polls, there may be a tendency to take statistics at face value, and fail to question the assumptions behind the numbers.

The possibility for data to be misused, or at least misleading, is exemplified by two ImClone press releases dated March 26, 2001. In one release, ImClone presented data from a preclinical study showing that 43 of 50 (86%) primary colorectal carcinoma tumors “demonstrated positive EGFR membrane staining.” As the cell membrane protein that Erbitux interacts with, EGFR must be present for Erbitux to be effective. In the other release, the company states that Erbitux “is designed to target and block the Epidermal Growth Factor Receptor (EGFR), which according to *studies*, can be expressed in as much as 86 percent of colorectal carcinoma” (emphasis added). However the American Cancer Society reported in 2000 that only 25-77 percent of colorectal cancers express EGFR (ImClone website info on Erbitux). It appears, therefore, that the company is announcing research results in one breath, and citing those results as gospel in the next. The statement may be literally true, but it is hardly the hallmark of the scientific process of peer review. In revealing trial results, companies run the risk that later trials, or even later analysis of the same trial, will render the original disclosure inaccurate. Fisher notes that it is important for courts to keep in mind that results are open to interpretation, and though FDA may find data submitted to be inadequate, this does not mean the company did not interpret, announce, and submit the results in good faith.<sup>175</sup> In *Padnes v. Scios*, the defendant made several announcements concerning a Phase II study to the effect that, among other things, its experimental drug, Auriculin, had a “statistically significant reduction in the *number of patients* requiring dialysis.”<sup>176</sup> Plaintiff’s found fault in this and other statements, and argued that, while factually accurate, the company’s disclosure was improper because, among other things, it failed to note that the study was randomized or double-blind, and “the difference in the dialysis *rates* between surviving control-group and surviving treatment-group patients was not statistically significant”<sup>177</sup> The court noted that “[r]easonable minds could differ with respect to the value of the [Phase II] study,” but, citing *In re MedImmune*, ruled that:

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<sup>175</sup>Fisher, 8 Mich. Telecomm. & Tech. L. Rev. 115 at 143-144.

<sup>176</sup>*Padnes v. Scios Nova, Inc.*, 1996 WL 539711 at \*2 (emphasis added, quoting Scios Nova’s 1993 Annual Report).

<sup>177</sup>*Id.*, 1996 WL 539711 at \*2 (emphasis added).



...where a company accurately reports the results of a scientific study, it is under no obligation to second-guess the methodology of that study. Medical researchers may well differ with respect to what constitutes acceptable testing procedures, as well as how best to interpret data garnered under various protocols. The securities laws do not impose a requirement that companies report only information from optimal studies, even if scientists could agree on what is optimal. Nor do they require that companies who report information from imperfect studies include exhaustive disclosures of procedures used, including alternatives that were not utilized and various opinions with respect to the effects of these choices on the interpretation of the outcome data.<sup>178</sup>

*MedImmune* also involved announcements concerning the results from a clinical trial. The company and its representatives made numerous statements, prior to the release of any trial data, about the importance of the trial results, including that “results of treatment . . . were highly statistically significant along all of the efficacy parameters,” and that “[w]e are quite enthusiastic about the results from the study and their implications for preventing [respiratory syncytial virus].”<sup>179</sup> Plaintiffs argued that such statements were materially misleading because flaws in the study design made it impossible to definitively establish the efficacy of the drug.<sup>180</sup> The court, however, concluded that although FDA raised questions about the results, the “[d]efendants and their affiliates developed data which they believed supported their conclusions regarding the drug’s efficacy.”<sup>181</sup> Similarly, in *In re Biogen Securities Litigation*, Biogen made several disclosures concerning results of a Phase II study of Hirulog – an anti-clotting agent – including a press release in which the company stated the study “showed a significant reduction in death and heart attacks among patients treated with Hirulog.”<sup>182</sup> What the company failed to mention was that the study results were not significant for any of the prospectively defined “endpoints,” and the only successful endpoint – reduction in death and heart attacks in subsection of the patient population receiving a high dose of the drug – was identified after the study, and data analysis, were complete.<sup>183</sup> Nevertheless, the court granted summary judgment for the defendant with respect to the press release, noting that Biogen did disclose that none of the four *primary* endpoints was met; finding immaterial the drug’s failure to meet the 24 secondary endpoints. The court also concluded that failure to disclose the retrospective nature of the “successful” endpoint was not enough to demonstrate fraud or recklessness required for liability.<sup>184</sup> More recently, the court in *DeMarco v. DepoTech Corp.* dismissed plaintiff’s 10b-5 claims regarding statements made by the defendant about the prospects for its experimental product, DepoCyt, a type of DepoFoam.<sup>185</sup> In its 1996 10-K, the company stated that it believed the product “will add additional value to [existing] drugs,” “[e]nhance the safety and efficacy” of existing drugs, and “may allow such drugs to be used in indications where they cannot currently be used because of the limitations of current delivery methods.”<sup>186</sup> Plaintiff’s also pointed to statements by DepoTech’s then President and CEO to the effect that DepoCyt would improve patients quality of life relative to current treatments, and a 1996 SEC Registration Statement in which the company also touted the safety and efficacy of DepoFoam.<sup>187</sup> The court pointed to several factors in rejecting

Several ImClone press releases comment on the results of Erbitux preclinical trials, some in which little or no data are actually presented. In response to results of a preclinical study for which no data was disclosed, ImClone scientists were quoted as saying “The activity of C225 [Erbitux] as a single agent in these xenograft studies is quite remarkable.”<sup>190</sup> In a later release in which two preclinical trials were discussed, with some data presented for one of the two trials, Sam Waksal stated, “These data in pancreatic cancer models provide further evidence that C225 as a single therapy or in combination with standard therapies can inhibit the growth and spread of a wide variety of cancer cells . . . .”<sup>191</sup> It is notable, however, that no reports of clinical trial results were found that did not include hard data concerning the percent, and often the actual number, of patients responding to therapy.

Similar problems arise from the publication of “hard” information such as rates of response and statistical significance, and study protocols. In this context courts seem to find it especially important that companies adequately define any potentially confusing technical information. In denying defendant’s motion for summary judgment in *In re Synergen, Inc. Securities Litigation*, the court concluded that the presentation of data on patient mortality in two contexts, without additional clarification, might have confused investors.<sup>192</sup> Defendants presented information on the number of patients that died during the 28-day trial (mortality rate), and the affect of higher dosage on the number of days a patient lived during the trial (survival curve), and reported that as to the survival curve there was a statistically significant response with  $p = 0.015$ . The court agreed with the plaintiff’s that an investor might have concluded that the measure of significance,  $p = 0.015$ , applied to the 28-day mortality rate, as well as the survival curve.<sup>193</sup> By contrast, in *DeMarco v.*

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<sup>190</sup>Press Release, ImClone Systems, Inc., ImClone Systems Incorporated Reports Data on its Cancer Therapeutic, C225 at American Association for Cancer Research Meeting (March 31, 1998), available at <http://www.imclone.com/news>.

<sup>191</sup>Press Release, ImClone Systems, Inc., ImClone Systems’ Lead Cancer Therapeutic, C225, Demonstrates Anti-Tumor Activity in Preclinical Models of Pancreatic Carcinoma (April 14, 1999), available at <http://www.imclone.com/news>.

<sup>192</sup>*In re Synergen, Inc. Sec. Litig.*, 863 F. Supp. at 1419.

<sup>193</sup>*Id.*, 863 F. Supp. at 1419.

*DepoTech Corp.*, defendant won a summary judgment motion against charges that investors were misled by the announcement of interim study results because the company used a different definition of “response” in reporting the interim results than was established in the original study protocol.<sup>194</sup> The court noted that each of the announcements explicitly defined “response,” and that plaintiff’s could not have relied on the original protocol definition because it was not public at the time the data was announced.<sup>195</sup> Fisher suggests four things companies can do to limit the risks of securities lawsuits based upon disclosure of hard information.<sup>196</sup> First, clearly describe information provided, and define any important terms. Second, have someone familiar with the trial protocol and results review disclosures before they are released. Third, avoid impromptu answers to questions from the media or investors. And finally, take affirmative steps to correct incorrect information reported by analysts or the media.

ImClone frequently revealed trial data for Erbitux in press releases that demonstrate some of the difficulties Fisher discusses. For example, in a Press Release for May 17, 1999, ImClone announced a 66 percent response rate for patients in a Phase Ib/IIa study of nine individuals with refractory advanced squamous cell head and neck carcinoma treated with C225 in combination with cisplatin, a chemotherapy agent. Reading further, however, the release notes that, while all six responders previously failed other treatment regimens, only three of the responders were refractory for cisplatin. Apparently, though the release does not say so explicitly, the other three responders were not refractory, meaning it would be impossible to determine if the response was due to Erbitux or cisplatin. Furthermore, the release provides no information about the treatment history of the three non-responders. The type of treatment previously received could affect the significance of the results. Nonetheless, the release quotes Erbitux discoverer, and ImClone board member, Dr. John Mendelsohn as saying, “The cisplatin study is a significant step in the development of C225 [Erbitux] because of the impressive response rate and because we observed that patients who have progressed

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<sup>194</sup>*DeMarco v. DepoTech Corp.*, 149 F. Supp. 2d 1212.

<sup>195</sup>*Id.*, 149 F. Supp. 2d at 1227-1228.

<sup>196</sup>Fisher, 8 Mich. Telecomm. & Tech. L. Rev. 115 at 158-159.

after cisplatin therapy respond when it is then combined with C225.”<sup>197</sup> A similar situation arises in a press release a year later, in which ImClone announced the results of a clinical trial of Erbitux in combination with cisplatin in 12 patients with head and neck carcinoma. The release states that all 12 patients responded, but then mentions, almost as an aside, that while all 12 patients were “refractory or relapsed following treatment with chemotherapy and/or radiation,” only a “majority” of the patients previously failed treatment with cisplatin.<sup>198</sup> Though there is no evidence that these disclosures are factually inaccurate, they seem to require investors to read between the lines in order to glean the full significance – or lack thereof – of the results. These disclosures raise concerns, but it must be acknowledged, as Fisher points out, that revealing trial results is a delicate balancing act between providing the investor enough information on which to buy or sell, while simplifying the analysis to avoid confusion. ImClone sought to walk that line by providing trial results, usually with some data and a simplified version of the trial protocol. In reporting data, the company was also consistent in disclosing the level of response of patients, and what that meant. For example, press releases announcing “partial” responses defined the term as “greater than 50 percent tumor regression,” which is the same definition agreed upon by ImClone and FDA in evaluating the 9923 trial.<sup>199</sup> The company also provided data for baseline comparisons when, for instance, announcing results of Erbitux used in combination with radiation therapy.<sup>200</sup>

While companies may choose to reveal test results, disclosure is usually not required; in some cases, however, companies may be obligated to reveal such information where failure to do so would make other disclosures

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<sup>197</sup>Press Release, ImClone Systems, Inc., ImClone Systems Presents Clinical Findings on C225 at American Society of Clinical Oncology Meeting (May 17, 1999), *available at* <http://www.imclone.com/news>.

<sup>198</sup>Press Release, ImClone Systems, Inc., ImClone Systems Presents Preliminary Results on Major Responses Using IMC-C225 in Combination with Chemotherapy in Patients with Refractory Cancers (May 22, 2000), *available at* <http://www.imclone.com/news>.

<sup>199</sup>*Id.*. See also Ron Winslow and Geeta Anand, *Laboratory Mixup: A Novel Cancer Drug, A Big Biotech Deal, And Now a Bitter Feud*, *supra* Note 15.

<sup>200</sup>Press Releases, ImClone Systems, Inc., ImClone Systems Incorporated Reports Data on its Cancer Therapeutic, C225, at American Society of Clinical Oncology Meeting (May 18, 1998), ImClone Systems Reports Data on Cancer Therapeutic, C225, at Annual Meeting of the American Society for Therapeutic Radiation and Oncology (October 27, 1998), *available at* <http://www.imclone.com/news>. Both releases note that published data for radiotherapy alone shows 30-40 percent response.

misleading.<sup>201</sup> This situation is most likely to arise in the case of negative test results that the company is unlikely to want to disclose. Courts have found evidence of scienter sufficient to survive summary judgment where the defendant knew of and failed to disclose negative test results while continuing to release positive statements regarding the product.<sup>202</sup> Courts have also found such circumstances to indicate materiality sufficient to survive summary judgment. Fisher notes that, in this context, courts have equated the test for materiality with determinations of statistical significance.<sup>203</sup> In *Synergen*, defendant made statements to the effect that the “[b]aseline characteristics were similar among treatment groups,” and therefore should not be a factor in the study.<sup>204</sup> In reviewing the results of the study, however, it was determined that, when controlling for the differences that did exist between the control and the experimental groups, some results went from being statistically significant to being insignificant.<sup>205</sup> In *Walsingham*, the court denied summary judgment to the defendant where the company did not disclose trial results for its medical device, but made positive statements about the device’s efficacy before and after the trial was complete. The court emphasized that the device was “essentially” the company’s only product, and noted that some of the defendant’s statements, made after the results were available, sought to rebuff criticism of the product’s effectiveness.<sup>206</sup> Prior to the Erbitux rejection, ImClone failed to reveal at least two pieces of hard information that might be considered material. First, the company did not disclose competing assessments of patient eligibility in the pivotal 9923 trial that would – and according to the FDA did – dramatically affect the significance of the results. Second, ImClone failed to disclose that, in light of the results of the single-agent study required by FDA, there was no statistically significant difference in the effects of Erbitux when used alone, and when used in concert with irinotecan in the 9923 trial.

<sup>201</sup>Fisher, 8 Mich. Telecomm. & Tech. L. Rev. 115 at 162-163.

<sup>202</sup>*Walsingham v. Biocontrol Tech., Inc.*, 66 F.Supp. 2d 669, 675 (W.D.Pa. 1998); see also *Kaplan v. Rose*, 49 F.3d 1363, 1375-80 (9<sup>th</sup> Cir. 1994) quoted in *In re Biogen Sec. Litig.*, 179 F.R.D. 25 (D. Mass. Sept. 4, 1997) at 36.

<sup>203</sup>Fisher, 8 Mich. Telecomm. & Tech. L. Rev. 115 at 161-162.

<sup>204</sup>*In re Synergen, Inc. Sec. Litig.*, 863 F. Supp. at 1416.

<sup>205</sup>*Id.*, 863 F. Supp. at 1419.

<sup>206</sup>*Walsingham v. Biocontrol Tech., Inc.*, 66 F.Supp. 2d at 677-678.

## Statements Concerning FDA Communications

Finally, problems may also arise when a company comments on communications with the FDA. During drug development, companies may communicate frequently with the agency over the design and implementation of trials, the results of those trials, and what more needs to be done for approval. Where FDA disagrees with the company over the adequacy of a trial, or the interpretation of trial data, “management must decide whether the FDA comments are material and whether the company’s positive report on the tests may be misleading if the company does not give at least some warning of the FDA position.”<sup>207</sup> In *MedImmune*, the court upheld a motion for summary judgment where the company failed to disclose concerns that FDA expressed about study design and implementation.<sup>208</sup> Noting that “[c]ontinuous dialogue between the FDA and the proponent of a new drug is the essence of the product license application process,” the court concluded “[m]ere questioning by the FDA imposed no duty upon Defendants either to trim back their opinions as to the efficacy of the drug or to report to the public the FDA staffer’s questions as they arose.”<sup>209</sup> The court further concluded that “[r]equiring ongoing disclosure of FDA’s questions would not only be disruptive to the review process; it could easily result in misleading the public more than not reporting the questions.”<sup>210</sup> In particular, the court pointed out that requiring disclosures of ongoing communications could send stock prices on a roller-coaster ride as questions were raised and answered during the course of drug development.<sup>211</sup> Courts have been less forgiving, however, where company statements run more directly against FDA concerns. Despite finding no duty to disclose concerns expressed by the agency, the *MedImmune* court denied defendant’s motion to dismiss as to the company’s statement that there was “absolutely no question about efficacy,” concluding

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<sup>207</sup>Fisher, 8 Mich. Telecomm. & Tech. L. Rev. 115 at 166.

<sup>208</sup>*In re MedImmune, Inc. Sec. Litig.*, 873 F. Supp. 953, 966 (D. Md. 1995).

<sup>209</sup>*Id.*, 873 F. Supp. at 966.

<sup>210</sup>*Id.*, 873 F. Supp. at 966.

<sup>211</sup>*Id.*, 873 F. Supp. at 966; see also *In re Biogen Sec. Litig.*, 179 F.R.D. 25 (D. Mass. 1997) (applying *MedImmune* where FDA expressed concerns about the adequacy of trial results).

that “it might well contain in its sweep a representation that the FDA had raised no question about the efficacy of the drug when in fact quite possibly it had.”<sup>212</sup> The court noted that “it is one thing to declare enthusiasm,” but “quite another to make a statement that . . . [the drug] was unquestionably efficacious,” and such a statement might be misleading.<sup>213</sup> Likewise, in *In re British Biotech PLC, et al.*, the SEC concluded that the company misled the public by continuing to make statements that the use of certain surrogate endpoints in a clinical trial demonstrated the efficacy of the drug against cancer, even after FDA sent the company a Notice of Violation informing the company that such statements were misleading.<sup>214</sup>

FDA apparently expressed concerns about the 9923 trial as early as August 2000, when it met with ImClone to discuss use of the trial to support a BLA.<sup>215</sup> The extent to which these concerns were conveyed is not clear. Although ImClone did not make statements to the public about its communications with FDA, there is evidence that company management may have downplayed the significance of FDA concerns in communications with ImClone’s partners, and potential partners. The Preliminary Committee Staff Report quotes an email from an unnamed drug company in which a company official states that, according to Harlan Waksal:

FDA has agreed that while [the 0141 study] is necessary for filing, it will not impact the approval of the combination in refractory. They [FDA] need to have the single agent activity per their regulations. They won’t use the small trial to compare RR [response rate] of the single agent to the combo, but will use it to help plan further development of C225 as a single agent if appropriate.<sup>216</sup>

In fact, the agency did compare response rates of the 0141 and 9923 trials in evaluating the Erbitux application, and the letter FDA sent requiring the study makes it clear that this is the point of the study.

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<sup>212</sup>*In re MedImmune, Inc. Sec. Litig.*, 873 F. Supp. at 967.

<sup>213</sup>*Id.*, 873 F. Supp. at 967.

<sup>214</sup>*In re British Biotech PLC, et al.*, SEC Administrative Proceeding File No. 3-9915).

<sup>215</sup>*Report of Dr. Weiss, supra* Note 55.



Similarly, the report quotes an internal BMS email from October 12, 2001, citing Sam Waksal with regard to the results of the 0141 trial:

I just had Sam Waksal on the phone re the single-agent data. Apparently it came out at 13% which he feels is half the C225 plus CPT-11 data. They have informed the FDA who were “pleased” and confirmed that they would be on for the Feb 28 ODAC (FDA’s Oncologic Drugs Advisory Committee). He reckons they will be on the market by March.<sup>217</sup>

But not only was FDA clearly not “pleased” by the results, in interviews by the staff, and at the hearings, no FDA personnel recalled speaking with Waksal about the results of the trial, and Erbitux was never on the February 2002 agenda for the ODAC meeting.<sup>218</sup>

## Part V: Going Forward

### What Really Went Wrong?

Enthusiasm expressed by ImClone’s management, and the considerable media attention, certainly contributed to investors overestimating the prospects for Erbitux. However both the company and the press frequently noted the uncertainties of the FDA approval process. In its cover story on Erbitux, Business Week pointed out that “a rule of thumb in the pharmaceutical industry is that only one out of 5,000 drug candidates discovered in labs is commercialized.”<sup>219</sup> “There is no guarantee that the FDA will approve the drug,” the article noted, “The agency often asks for more data, adding many months to the process.” The more likely candidates for misleading investors, it would seem, are ImClone’s agreement with Bristol-Myers

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<sup>218</sup>*Id.*

<sup>219</sup>Catherine Arnst, *supra* Note 13.

Squibb, and the company's presentation of clinical trial results.

Certainly an important factor in the rise in ImClone's stock price in the latter part of 2001 was the deal with Bristol-Myers Squibb. Investors no doubt considered a \$2 billion investment by one of the world's most respected pharmaceutical companies to be a strong endorsement of Erbitux. What investors were not aware of were the serious concerns BMS had about the Erbitux BLA. Internal BMS communications indicate that the company perceived several potential problems with the application: (1) BMS lacked data from the single agent study, and no drug had ever been approved through fast track based solely upon data in combination studies; (2) radiology review of 27 alleged responders in the 9923 study suggested the response rate could be lower than the required 15 percent; and (3) the number of patients in the 9923 study meeting the eligibility requirements might be below 100, making it unlikely the study could serve as the basis for an accelerated approval application.<sup>220</sup> There were also concerns that "the dose is questionable for refractory patients, and the safety margin for the early stage patient, has not been determined."<sup>221</sup>

But while BMS officials expressed some concerns that the venture was "a very high risk opportunity," it wasn't until it re-examined the 9923 study data after the RTF letter that it recognized the severity of the problems with the study.<sup>222</sup> Defending BMS's decision to invest at the Congressional hearing, Laurie Smaldone of BMS testified, "[t]here was data that was conducted by reputable oncologists, already presented to ASCO [American Society of Clinical Oncologists], which is a premier Scientific Congress for Oncology, that validated our understanding of the data."<sup>223</sup> She also noted that while BMS due diligence revealed some potential problems, ImClone was already in the fast track process, and in advanced discussions with the FDA.<sup>224</sup> Nonetheless, it is concerning that a company of the stature of BMS entered into a \$2 billion

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<sup>220</sup> *Hearings*, *supra* Note 18 at 45 (Preliminary Committee Staff Report).

<sup>221</sup> *Hearings*, *supra* Note 18 at 93 quoting internal Bristol-Myers Squibb email.

<sup>222</sup> Peter Landers and Chris Adams, *Potent Mix: Drug News, Stock Trading*, Wall St. J., June 14, 2002, at C1; *Hearings*, *supra* Note 18 at 44-45, 92.

<sup>223</sup> *Hearings*, *supra* Note 18 at 82 (Testimony of Laurie Smaldone, Senior Vice President, Global Regulatory Sciences, Bristol-Myers Squibb Co.).

<sup>224</sup> *Hearings*, *supra* Note 18 at 82 (Testimony of Laurie Smaldone, Senior Vice President, Global Regulatory Sciences, Bristol-Myers Squibb Co.).

licensing agreement based upon such a basic misconception of either the data itself or its adequacy.

The ImClone affair also raises serious questions about allowing companies to determine, more or less unfettered, what trial results are released, when they are released, and how they are presented. It is true that ImClone's announcements are not unusual for a biotechnology company, nor was the company irrationally exuberant – to borrow a phrase – in discussing trial results, and the future of Erbitux. When presenting data from clinical studies the company generally provided response rates, basic protocol information, and often other information to put the results in context.<sup>225</sup> The company certainly put its best foot forward, but it also consistently warned of the dangers of relying on forward-looking statements. Nor is it determinative that later analysis of the 9923 study came to very different conclusions. Disputes over the results of the 9923 study serve to illustrate the considerable subjectivity that can affect data interpretation.<sup>226</sup> While the extent of disagreement may be unusual, study results are always open to interpretation. But the fact that ImClone's presentation of its data was not unusual, or necessarily inaccurate, does not mean it was not misleading. Investors must make numerous assumptions about the conduct and analysis of clinical trials that, in this case, turned out to be erroneous. When data for the 9923 study were initially disclosed at the May 2001 annual meeting of the American Society of Clinical Oncology the presentation was limited, and many of the key issues in the study were asserted by ImClone without proof, and remained unreviewed, and

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<sup>225</sup> See Press Releases, ImClone Systems, Inc., ImClone Systems Incorporated Reports Data on its Cancer Therapeutic, C225, at American Society of Clinical Oncology Meeting (May 18, 1998), ImClone Systems Presents Clinical Findings on C225 at American Society of Clinical Oncology Meeting (May 17, 1999), ImClone Systems Presents Preliminary Results on Major Responses Using IMC-C225 in Combination with Chemotherapy in Patients with Refractory Cancers (May 22, 2000), ImClone Systems Presents Clinical Findings on the Follow Up of Patients Treated with IMC-C225 in Combination with Radiation (May 23, 2000), ImClone Systems Announces Achievement of a 22.5 Percent Response Rate in Its Phase II Clinical Study of IMC-C225 and Chemotherapy in Patients with Refractory Colorectal Cancer (May 12, 2001).

<sup>226</sup> Report of Dr. Weiss, *supra* Note 55. Independent review of study data by the study investigators, by BMS, and by an Independent Response Assessment Committee (IRAC) assembled by ImClone, revealed numerous disagreements. Overall, the investigators reported 23 partial responses (greater than 50% regression), the IRAC reported 27 partial responses, and BMS recategorized as “stable disease” 8 patients the IRAC labeled partial response. The IRAC and the investigators only agreed on 20 patients with partial response. The IRAC and BMS only agreed on 16 patients with partial response. There were also 38 patients where the category of the disease status prior to study entry (ie, progressive or stable) was in disagreement between IRAC and the investigators.

uncontroverted, until the FDA issued the RTF letter seven months later.<sup>227</sup> This may create an undue sense of credibility that could mislead investors.

## Revamping the Approval Process and Improving Monitoring

These and other concerns surfaced in the wake of the Erbitux rejection and the subsequent investigations, and Congress and the FDA have since sought to address many of them. The June 2002 reauthorization of the Prescription Drug User Fee Act of 1992 (PDUFA) requires CBER and CDER to draft a joint guidance on how the FDA defines good review management principles, and emphasizes the need for effective communications between the agency and drug sponsors.<sup>228</sup> The FDA also agreed to increased meetings with companies in which minutes are kept, and during which agency officials offer “the best interpretation we can along scientific lines and medical lines of what we expect the company to do.”<sup>229</sup>

In September 2002, the FDA undertook a plan to transfer review of “certain therapeutic biologics from CBER to CDER,” including review of monoclonal antibodies such as Erbitux.<sup>230</sup> The consolidation will also move several hundred employees from CBER to CDER. FDA Deputy Commissioner Lester Crawford testified that he concluded such consolidation “would promote efficiency and consistency within the agency.”<sup>231</sup> FDA announced completion of the final phase of planning for the consolidation on March 17, 2003, and set a target implementation date of June 30, 2003.

These changes do not alter the basic authority of the FDA, however, and aside from hopefully creating more consistency in the drug approval process – certainly an important goal – do not help to prevent future

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<sup>227</sup>Press Release, ImClone Systems, Inc., ImClone Systems Announces Achievement of a 22.5 Percent Response Rate in its Phase II Clinical Study of IMC-C225 and Chemotherapy in Patients with Refractory Colorectal Cancer, *supra* Note 68. *See also Report of Dr. Weiss, supra* Note 55.

<sup>228</sup>*Hearings, supra* Note 18 at 227-228.

<sup>229</sup>*Id.* at 229 (Testimony of Dr. Lester Crawford, Deputy Director, Food and Drug Administration).

<sup>230</sup>*Id.* at 228 (Testimony of Dr. Lester Crawford, Deputy Director, Food and Drug Administration).

<sup>231</sup>*Id.* at 228 (Testimony of Dr. Lester Crawford, Deputy Director, Food and Drug Administration).

disasters of the type Erbitux created. More must be done, therefore, to ensure that history does not repeat itself.

The problems presented by the BMS agreement are probably impossible to police. The decision to enter into a licensing agreement is purely the company's, and the fact that its due diligence was inadequate, or that management made a bad judgment call, is not in the purview of the SEC – absent breach of management's duty of care – much less the FDA. The SEC does require that companies reveal some information about such transactions, but it cannot require disclosure of every internal memo expressing doubt or concern. To do so would deter companies from sharing confidential information in the first place, and add even more uncertainty to collaborative agreements. The reality is that some risk and uncertainty is a part of investing, and is probably better dealt with by individual investors diversifying their portfolios than by requiring disclosure of every minutiae of a company's affairs.

Problems presented by the announcement of clinical trial results may be easier to address, though they cannot be eliminated. To help resolve this problem a company choosing to present data documenting response rates could be required to provide other information to put those results in context. For example, basic statistical analysis along with an explanatory note about the uncertainties of such analysis, and of data interpretation, would give investors a more accurate picture of the importance of trial data. The FDA or SEC might mandate a cookie-cutter disclaimer for all disclosures of trial data, akin to the Surgeon General's warning on packs of cigarettes. Requiring certain contextual information about related therapies – whether part of the study or not – would also help by giving investors a basis of comparison. These solutions will not eliminate the heavy reliance on data, but they should reduce the uncertainty.

Of course it is still not clear whether the FDA or the SEC should be responsible for enforcement. Disclosures made prior to the initiation of FDA review of a licensing application will be difficult, if not impossible for that agency to police, and therefore the SEC seems the more natural choice. The SEC, however, could

not be expected to pass on the scientific accuracy of many disclosures. A compromise might give the SEC primary authority to monitor disclosures, but require companies to simultaneously submit to the FDA data in support of any clinical trial results the company chooses to announce. All of this data will eventually be disclosed if the company seeks marketing approval, so the requirement should not impose an excessive burden on companies. Nor would the FDA be required to review the information at the time of the announcement, but the agency would have easy access to the data should it, or the SEC, determine something might be amiss in a company's disclosures. This is not a sure-fire solution, and it would certainly require increasing the FDA's resources, but it might force companies to be more discreet when discussing study results.

Again, however, it must be noted that regulatory oversight has its limits. No matter how much information investors are provided with, they still rely on the company to ensure the information is accurate, and no matter how much the FDA chooses to regulate the development of clinical trials, it cannot see to it that protocol is always followed, and data always properly documented. The lesson of the ImClone affair may be that investors should be more cautious, and recognize the considerable uncertainty and complexity inherent in drug development. Biotechnology stocks are not for the faint of heart, and risk-averse investors must take adequate precautions by diversifying their portfolios, or simply avoiding the biotech sector all together.

At the congressional hearings, it was suggested that perhaps the FDA should be less restrained in its ability to disclose information to the public. This would require some changes to current law to loosen disclosure rules. Doing so could help in the future, but it has several limitations. First, expanding the FDA's authority would not affect disclosures made by companies prior to the commencement of FDA review. Second, as already discussed, the FDA would be hard pressed to muster the resources to take on the task of monitoring company disclosures.<sup>232</sup> Third, disclosure of information before the FDA is able to fully review and evaluate an application could do more harm than good to the goal of certainty in financial markets.<sup>233</sup> Because some

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<sup>232</sup>Geeta Anand and Chris Adams, *ImClone Incident Spurs Demands For Greater Disclosure From FDA*, *supra* Note 5 citing an FDA official.

<sup>233</sup>*Id.*

applications, including ImClone's are submitted piecemeal over a period of months, data acquired early on could be negated by data received later, and requiring the agency to reveal such data could send biotech stocks on a roller coaster ride. However more limited disclosure might be appropriate once the application is complete and agency officials have taken a preliminary pass at the data. In particular, the FDA should not sit on a final decision to issue an RTF letter any longer than absolutely necessary; a problem that hopefully will be eliminated when review is consolidated in CDER.<sup>234</sup>

As noted earlier, however, the FDA already has the tools to deal with many of the problems of the sort ImClone raised. The agency could be more aggressive in issuing public rebukes, as it did in the SuperGen case.<sup>235</sup> It could also rely more on the SEC. Dr. Crawford testified that the FDA has undertaken "a systematic review" of its interactions with the SEC, which hopefully will put in place procedures to address future problems.<sup>236</sup> The role of the SEC may be further enhanced by changes being considered by that agency. The ImClone affair has prompted the SEC to take another look at the types of disclosures it requires from companies. The agency is considering requiring companies to disclose some of the content of discussions with the FDA in Form 8-K reports.<sup>237</sup> Extending reporting requirements to include this type of information could prove beneficial, but it will likely be difficult to clearly define the boundaries of required disclosure. The definition of materiality in this context must be carefully delineated to include serious FDA concerns, but exclude routine agency suggestions and requests for information. Litigation will certainly ensue.

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<sup>234</sup>Geeta Anand, Jerry Markon and Chris Adams, *Biotech Bust: ImClone's Ex-CEO Arrested, Charged With Insider Trading*, Wall St. J., June 13, 2002, at A1.

<sup>235</sup>*Supra* at 30-31.

<sup>236</sup>*Hearings, supra* Note 18 at 229 (Testimony of Dr. Lester Crawford, Deputy Director, Food and Drug Administration).

<sup>237</sup>Harold S. Bloomenthal and Samuel Wolff, *Securities and Federal Corporate Law* (2d ed.), Sect. 7:36.19.

## The Future of ImClone and Erbitux

Things only seemed to get worse for ImClone after Erbitux was rejected, and 2002 was a tumultuous year for the company. In March 2002, ImClone announced it had agreed to revised terms for its licensing agreement with BMS that substantially reduced future incentive payments.<sup>238</sup> Several magazines and newspapers ran stories alleging Sam Waksal had a history of improper behavior in the scientific community, and was forced to leave several labs for a variety of reasons, including misleading and falsified scientific work.<sup>239</sup> Dr. Waksal resigned from ImClone in May, and in October pled guilty to six of the 13 counts against him for insider trading and other crimes.<sup>240</sup> ImClone has sued Sam Waksal to recover money paid him in his separation agreement with the company, because of his failure to cooperate with the investigation into his conduct.<sup>241</sup> But ImClone is taking steps to right itself. It has created a Disclosure Committee to review public disclosures and ensure they are appropriate, and adopted a code of business conduct and ethics.<sup>242</sup> In April of 2002 the ImClone board adopted new policies requiring 16 officers to file reports of their transactions under SEA §16, and ending consulting arrangements with directors.<sup>243</sup> The company also put in place procedures to comply with the Sarbanes-Oxley law.<sup>244</sup>

Things are even looking up for Erbitux. Despite the FDA rejection, Erbitux is not without its proponents, and even FDA officials admitted the failure of the company's BLA was more about the conduct of its trial

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<sup>238</sup>Press Release, ImClone Systems, Inc., ImClone Systems and Bristol-Myers Squibb Announce Revised Terms of Commercialization Agreement for ERBITUX (March 5, 2003). See also Geeta Anand, *ImClone Systems and Bristol-Myers Reach an Accord*, Wall St. J., March 6, 2003, at A2.

<sup>239</sup>Andy Serwer and Julia Boorstein, *The Socialite Scientist*, Fortune Magazine, April 15, 2002 at 152; Geeta Anand, *In Waksal's Past: Repeated Ousters*, Wall St. J., Sept. 27, 2002, at A1; *Hearings*, *supra* Note 18 at 283.

<sup>240</sup>Jerry Markon and Geeta Anand, *Waksal Pleads Guilty as U.S. Widens Probe*, Wall St. J., Oct. 16, 2002, at C1.

<sup>241</sup>*Hearings*, *supra* Note 18 at 251 (Testimony of Paul Kopperl, Director, ImClone Systems, Inc.).

<sup>242</sup>Press Release, ImClone Systems, Inc., ImClone Systems Incorporated Announces Board Changes (March 4, 2003), available at <http://www.imclone.com/news>.

<sup>243</sup>*Hearings*, *supra* Note 18 at 251 (Testimony of Paul Kopperl, Director, ImClone Systems, Inc.).

<sup>244</sup>*Id.* at 255 (Testimony of Harlan Waksal, CEO, ImClone Systems, Inc.).



than the quality of its drug. ImClone has undertaken several Phase II and III clinical trials of Erbitux alone and in conjunction with other drugs. The results of a 330 patient study in refractory colorectal cancer patients, conducted by ImClone's European partner Merck KGaA will be announced at this year's annual meeting of the American Society of Clinical Oncology in June.<sup>245</sup> Two thirds of the patients received Erbitux and irinotecan, and the other third received only Erbitux.<sup>246</sup> In a statement, Merck KGaA's Chief Executive Bernhard Scheuble said a recent assessment of trial data by independent scientists left the company optimistic that it would file for European regulatory approval this year.<sup>247</sup> "The good result from the external review was as expected, because why should an external review give a different view than an internal one?"<sup>248</sup> Perhaps he should ask Sam Waksal.

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<sup>245</sup>Merck KGaA is unrelated to the American drug company, Merck.

<sup>246</sup>Andrew Pollack, *German Inquiry Into a Drug Helps Lift ImClone Shares*, N.Y. Times, March 29, 2003, available at <http://www.nytimes.com>.

<sup>247</sup>James Mackenzie and Ben Hirschler, *Merck says Erbitux on track after positive review*, Reuters, March 28, 2003, available at [http://biz.yahoo.com/rc/030328/health\\_merck\\_erbitux\\_4.html](http://biz.yahoo.com/rc/030328/health_merck_erbitux_4.html).

<sup>248</sup>*Id.*